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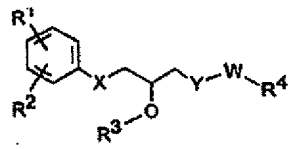
Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist; Veröffentlichung wird wiederholt falls Änderungen eintreffen.

(54) Title: BENZAMINE DERIVATIVES

(54) Bezeichnung: BENZAMIDINDERIVATE ALS KOAGULATIONSFAKTOR-XA-HEMMER



(1)

(57) Abstract

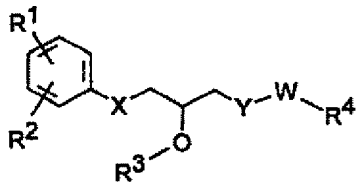
The invention relates to novel compounds of formula (1) wherein X, Y, W, R^1, R^2, R^3 and R^4 have the meaning cited in Claim 1. The inventive compounds are inhibitors of coagulation factor Xa and can be used in prophylaxis and/or therapy for thromboembolic diseases.

(57) Zusammenfassung

Neue Verbindungen der Formel (1), worin X, Y, W, R^1, R^2, R^3 und R^4 die in Patentanspruch 1 angegebene Bedeutung haben, sind Inhibitoren des Koagulationsfaktors Xa und können zur Prophylaxe und/oder Therapie von thromboembolischen Erkrankungen eingesetzt werden.

BENZAMIDINE DERIVATIVES AS COAGULATION FACTOR XA INHIBITOR

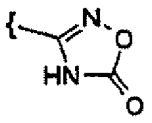
The invention relates to compounds of the formula I



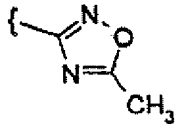
I

in which

R^1 is $-C(=NH)-NH_2$ which can also be monosubstituted by -COA, $-CO-[C(R^5)_2]_m-Ar$, -COOA, -OH or by a conventional amino-protective group,



or



,

R^2 is H, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NR^5COA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^5$, $CON(R^5)_2$, CONHAr, COR^5, COAr, $S(O)_nA$ or $S(O)_nAr$,

R^3 is R^5 or $-[C(R^5)_2]_m-COOR^5$,

R^3 and X together are also -CO-N-, thus forming a 5-membered ring, where R^3 is -C=O and X is N,

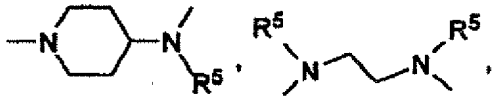
R^4 is A, cycloalkyl, $-[C(R^5)_2]_mAr$, $-[C(R^5)_2]_mHet$ or $-CR^5=CR^5-Ar$,

R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y is O, NR^5, $N[C(R^5)_2]_m$-Ar, $N[C(R^5)_2]_m$-Het,

$N[C(R^5)_2]_m$-$COOR^5$,



$N[C(R^5)_2]_m$-$CON(R^5)_2$, $N[C(R^5)_2]_m$-$CONR^5Ar$ or $N[C(R^5)_2]_m$-$CONAr_2$,

W is a bond, $-SO_2-$, -CO-, or $-CONR^5-$,

A is alkyl having 1-20 C atoms in which one or two CH_2 groups can be replaced by O or S atoms or by $-CR^5=CR^5-$ groups and/or 1-7 H atoms can be replaced by F,

Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, Ar', OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^5$, $CON(R^5)_2$, CONHAr', COR^5, COAr', $S(O)_nA$ or $S(O)_nAr$,

Ar' is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, $COOR^5$, $CON(R^5)_2$, COR^5 or $S(O)_nA$,

Het is a mono- or bicyclic saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different hetero atoms such as nitrogen, oxygen and sulfur and which is unsubstituted or mono- or polysubstituted by Hal, A, Ar', OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOAr' and/or carbonyl oxygen,

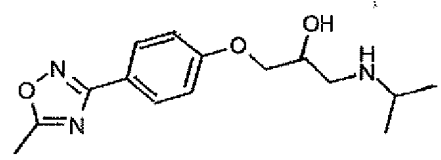
Hal is F, Cl, Br or I,

m is 0, 1, 2, 3 or 4,

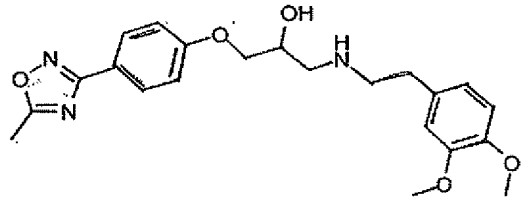
n is 0, 1 or 2,

and salts thereof,

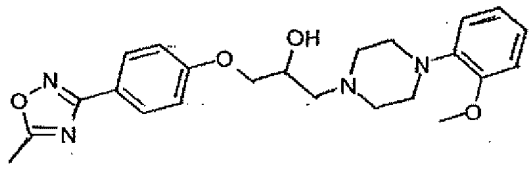
with the proviso that the following compounds are excluded:



1-isopropylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol;



1-[2-(3,4-dimethoxy-phenyl)-ethylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol; and



1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol.

The invention also provides the optically active forms, the racemates, the diastereomers and the hydrates and solvates of these compounds.

The invention was based on the object of discovering novel compounds having valuable properties, in particular those which can be used for preparing medicaments.

It has been found that the compounds of the formula I and their salts have very useful pharmacological properties, coupled with good tolerability. In particular, they have factor Xa-inhibiting properties and can therefore be employed for combating and preventing thromboembolic disorders such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

Aromatic amidine derivatives having antithrombotic action are known, for example, from EP 0 540 051 B1. Cyclic guanidines for the treatment of thromboembolic disorders are described, for example, in WO 97/08165. Aromatic heterocycles having factor Xa-inhibiting activity are known, for example, from WO 96/10022.

The antithrombotic and anticoagulant effect of the compounds according to the invention is attributed to the inhibiting action on the activated coagulation protease, known under the name factor Xa, or to the inhibition of other activated serine proteases such as factor VIIa, factor IXa or thrombin.

inhibition of other activated serine proteases such as factor VIIa, factor IXa or thrombin.

Factor Xa is one of the proteases which is involved in the complex process of blood coagulation. Factor Xa catalyses the conversion of prothrombin into thrombin. Thrombin cleaves fibrinogen into fibrin monomers which, after crosslinking, contribute fundamentally to thrombus formation. An activation of thrombin can result in the occurrence of thromboembolic disorders. An inhibition of thrombin, however, can inhibit the fibrin formation involved in the formation of a thrombus.

The inhibition of thrombin can be measured, for example, by the method of G. F. Cousins et al. in *Circulation* **1996**, *94*, 1705-1712.

Inhibition of factor Xa can thus prevent thrombin formation.

The compounds of the formula I according to the invention and their salts intervene in the blood coagulation process by inhibiting factor Xa and thus inhibit the formation of thrombi.

The compounds of the formula I according to the invention can furthermore function as inhibitors of the blood clotting factors factor VIIa, factor IXa and thrombin of the blood clotting cascade.

The inhibition of factor Xa by the compounds according to the invention and the measurement of the anti-coagulating and antithrombotic activity can be determined by customary in vitro or in vivo methods. A suitable method is described, for example, by J. Hauptmann et al. in *Thrombosis and Haemostasis 63, 220-223 (1990)*.

The inhibition of factor Xa can also be measured, for example, by the method of T. Hara et al. in *Thromb. Haemostas. 71, 314-319 (1994)*.

The blood clotting factor VIIa initiates, after binding to tissue factor, the extrinsic part of the blood clotting cascade and contributes to the activation of factor X to factor Xa. An inhibition of factor VIIa thus prevents the formation of factor Xa and thus a subsequent formation of thrombin.

The inhibition of factor VIIa by the compounds according to the invention and the determination of the anticoagulant and antithrombotic activity can be determined using customary in vitro or in vivo methods. A customary process for measuring the inhibition of factor VIIa is described, for example, by H. F. Ronning et al. in *Thrombosis Research* **1996**, *84*, 73-81.

The compounds of the formula I can be employed as medicaments in human and veterinary medicine, in particular for combating and preventing thromboembolic disorders such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

The invention provides the compounds of the formula I and their salts, and also a process for preparing compounds of the formula I according to Claim 1 and their salts, characterized in that

a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent, by

   i) liberating an amidino group from its oxadiazole derivative by hydrogenolysis,

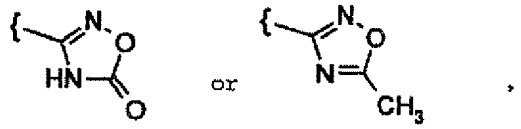
   ii) replacing a conventional amino-protective group by treatment with a solvolysing or hydrogenolysing agent with hydrogen or

liberating an amino group which is protected by a conventional protective group,

or

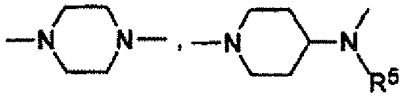
b) that for preparing compounds of the formula I

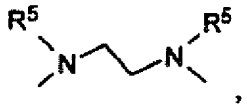
in which R^1 is



,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or

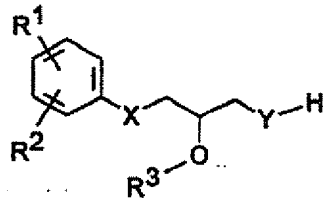


,

W is $-SO_2-$ or -CO-,

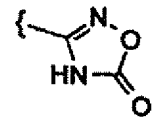
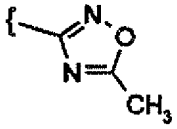
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II

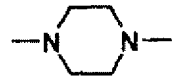
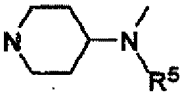


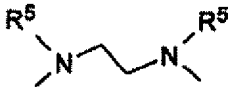
II

in which

R^2 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  ,  or

 ,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula III

$$R^4\text{-}W\text{-}L \qquad III$$

in which

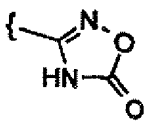
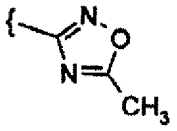
W is $-SO_2-$ or -CO-,

R^4 is as defined in Claim 1,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

or

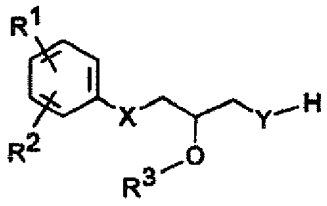
c) that for preparing compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
W is a bond,

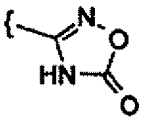
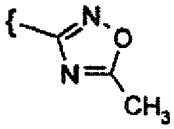
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
and R^2 is as defined in Claim 1,

is reacted with a compound of the formula IV

$$R^4\text{-W-OH} \qquad \text{IV}$$

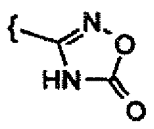
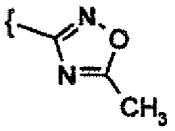
in which

W is a bond,

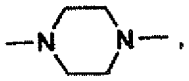
and R^4 is as defined in Claim 1,

or

d) that for preparing compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

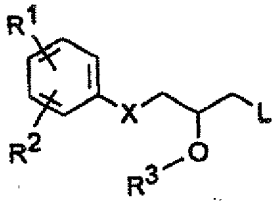
W is a bond,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$,

m is 0,

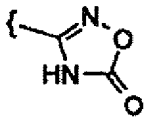
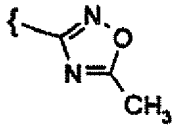
and R^2 is as defined in Claim 1,

a compound of the formula V



V

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^2 is as defined in Claim 1,

is reacted with a compound of the formula VI

$$R^4\text{-}W\text{-}Y\text{-}H \qquad VI$$

in which

W is a bond,

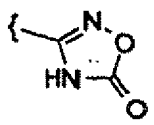
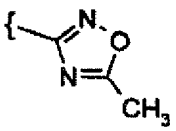
Y is  ,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$ and

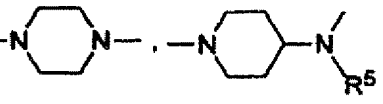
m is 0,

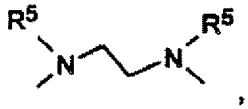
or

e) that for preparing compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

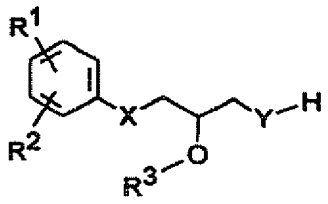
Y is NR^5,  or



W is -CONH-,

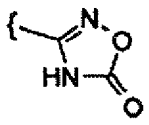
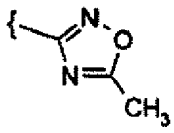
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II

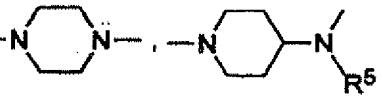


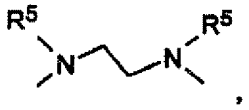
II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or



and R^2 and R^5 are as as defined in Claim 1,

is reacted with a compound of the formula VII

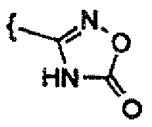
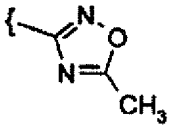
$$R^4\text{-}N{=}C{=}O \qquad \text{VII}$$

in which

R^4 is as defined in Claim 1,

or

f) that for preparing compounds of the formula I

in which R^1 is  or  ,

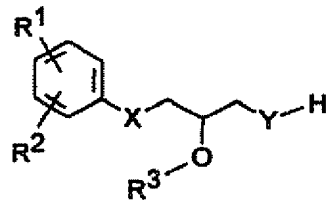
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m\text{-}COOR^5$,

W is SO_2,

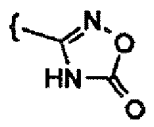
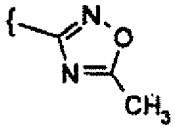
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula VIII

$$R^4\text{-}SO_2\text{-}L \qquad \text{VIII}$$

in which

L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^4 is as defined in Claim 1,

or

g) that for preparing compounds of the formula I

in which

X is NH and

R^3 is H

and R^1, R^2, R^4, Y and W are as defined in Claim 1,

these compounds are liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolysing agent,

or

h) that for preparing compounds of the formula I

in which R^1 is $-C(=NH)-NH_2$,

a cyano group is converted into an amidino group,

or

i) in a compound of the formula I, one or more radicals Y, R^1, R^2, R^3 and/or R^4 are converted into one or more radicals R^1, R^2, R^3 and/or R^4,

by, for example,

i) hydrolysing an ester group to give a carboxyl group,

ii) reducing a nitro group,

iii) acylating an amino group,

and/or

k) converting a base or acid of the formula I into one of its salts.

For all the radicals which occur several times, such as, for example, R^5, the meanings thereof are independent of one another.

Hereinabove and hereinbelow, the radicals or parameters L, W, X, Y, R^1, R^2, R^3, R^4, R^5, m and n have the meanings given for the formulae I to VIII, unless expressly stated otherwise.

Solvates is [sic] addition compounds with, for example, organic inert solvents, such as, for example, with alcohols such as methanol, ethanol or propanol.

In the above formulae, A is alkyl, is linear or branched, and has 1 to 20, preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 C atoms. A is preferably methyl, furthermore ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl, furthermore also pentyl, 1-, 2- or 3-methylbutyl, 1,1-, 1,2- or 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-, 2-, 3- or 4-methylpentyl, 1,1-, 1,2-, 1,3-, 2,2-, 2,3- or 3,3-dimethylbutyl, 1- or 2-ethylbutyl, 1-ethyl-1-methylpropyl, 1-ethyl-2-methylpropyl, 1,1,2- or 1,2,2-trimethylpropyl, heptyl, octyl, nonyl or decyl.
A is furthermore, for example, trifluoromethyl, pentafluoroethyl, allyl or crotyl.

OR^5 is OH, OA or benzyloxy, with OA preferably being methoxy, ethoxy, propoxy, butyloxy or hexyloxy.

Cycloalkyl is preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. Cycloalkyl is, for example, also the radical of a bicyclic terpene, such as, for example, 3-menthyl; particular preference is given to the camphor-10-yl radical.

COR^5 is acyl and is preferably formyl, acetyl, propionyl, furthermore also butyryl, pentanoyl or hexanoyl.

Hal is preferably F, Cl or Br, but also I.

R^2 is preferably H, fluorine, chlorine, bromine, iodine, hydroxyl, methoxy, ethoxy, propoxy, nitro, amino, methylamino, dimethylamino, ethylamino, diethylamino, acetamido, sulfonamido, methylsulfonamido, phenylsulfonamido, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, phenylsulfinyl, phenylsulfonyl, cyano, carboxyl, methoxycarbonyl, ethoxycarbonyl, furthermore also acyl or benzoyl.

R^2 is, in particular, H.

R^3 is preferably A, benzyl, CH_2COOH or CH_2COOA, but in particular H.

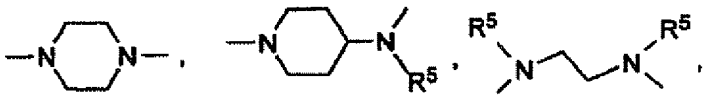
R^4 is preferably, for example, A, cycloalkyl, Ar, CH_2Ar, CH_2CH_2Ar, CH_2Het, CH_2CH_2Het or CH=CH-Ar.

R^5 is H, A or benzyl, but in particular H.

X is O, NH, NA or N-benzyl, furthermore also CH_2.

R^3 and X together are also -CO-N-, thus forming, together with the $-CH_2-CH-O-$ unit, a five-membered ring.

Y is preferably, for example, O, NH, N-methyl, N-ethyl, N-Ar, $N-CH_2-Ar$, N-Het, $N-CH_2-Het$, N-COOA, $N-CH_2-COOA$, $N-CH_2-COOH$, $N-CH_2-COObenzyl$,



NCH_2-CONH_2, $NCH_2-CONHA$, NCH_2-CONA_2, NCH_2-CONR^5Ar or $NCH_2-CONAr_2$.

W is preferably, for example, a bond, $-SO_2-$ or -CO-, furthermore also -COO- or -CONH-.

Ar is preferably unsubstituted phenyl or naphthyl, furthermore preferably naphthyl or phenyl which is mono-, di- or trisubstituted, for example by A, fluorine, chlorine, bromine, iodine, hydroxyl, methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy,

benzyloxy, phenethyloxy, methylthio, ethylthio, methylsulfinyl, ethylsulfinyl, methylsulfonyl, ethylsulfonyl, phenylsulfinyl, phenylsulfonyl, nitro, amino, methylamino, ethylamino, dimethylamino, diethylamino, formamido, acetamido, propionylamino, butyrylamino, methylsulfonamido, ethylsulfonamido, propylsulfonamido, butylsulfonamido, phenylsulfonamido, (4-methylphenyl)sulfonamido, carboxymethoxy, carboxyethoxy, methoxycarbonylmethoxy, methoxycarbonylethoxy, hydroxymethoxy, hydroxyethoxy, methoxyethoxy, carboxyl, methoxycarbonyl, ethoxycarbonyl, cyano, phenylaminocarbonyl, acyl or benzoyl, furthermore also biphenyl.

Ar is therefore preferably, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)-phenyl, o-, m- or p-acetylphenyl, o-, m- or p-formylphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl, o-, m- or p-methylsulfonylphenyl, o-, m- or p-(phenylsulfonamido)phenyl, o-, m- or p-(methylsulfonamido)-phenyl, o-, m- or p-methylthiophenyl, furthermore preferably 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-difluorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dichlorophenyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dibromophenyl, 2,4- or 2,5-dinitrophenyl, 2,5- or 3,4-dimethoxyphenyl, 3-nitro-4-chlorophenyl, 3-amino-4-chloro-, 2-amino-3-chloro-, 2-amino-4-chloro-, 2-amino-5-chloro-, or 2-amino-6-chlorophenyl, 2-nitro-4-N,N-dimethylamino- or 3-nitro-4-N,N-dimethylaminophenyl, 2,3-diaminophenyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,6- or

3,4,5-trichlorophenyl, 2,4,6-trimethoxyphenyl, 2-hydroxy-3,5-dichlorophenyl, p-iodophenyl, 3,6-dichloro-4-aminophenyl, 4-fluoro-3-chlorophenyl, 2-fluoro-4-bromophenyl, 2,5-difluoro-4-bromophenyl, 3-bromo-6-methoxyphenyl, 3-chloro-6-methoxyphenyl, 3-chloro-4-acetamidophenyl, 3-fluoro-4-methoxyphenyl, 3-amino-6-methylphenyl, 3-chloro-4-acetamidophenyl or 2,5-dimethyl-4-chlorophenyl.

Ar is very particularly preferably phenyl which is unsubstituted or mono-, di- or trisubstituted by amino, OR^5, Hal, CN, alkyl having 1-10 carbon atoms, CF_3, CH_3SO_2, OCF_3, acetamido, $-C(=NH)-NH_2$, methoxycarbonyl or ethoxycarbonyl, furthermore naphthyl which is mono-substituted by Hal, dimethylamino or alkoxy having 1-6 carbon atoms and also unsubstituted biphenyl.

Ar' is in particular, for example, phenyl or naphthyl, furthermore preferably, for example, o-, m- or p-tolyl, o-, m- or p-ethylphenyl, o-, m- or p-propylphenyl, o-, m- or p-isopropylphenyl, o-, m- or p-tert-butylphenyl, o-, m- or p-hydroxyphenyl, o-, m- or p-nitrophenyl, o-, m- or p-aminophenyl, o-, m- or p-(N-methylamino)phenyl, o-, m- or p-acetamidophenyl, o-, m- or p-methoxyphenyl, o-, m- or p-ethoxyphenyl, o-, m- or p-carboxyphenyl, o-, m- or p-methoxycarbonylphenyl, o-, m- or p-(N,N-dimethylamino)phenyl, o-, m- or p-(N-ethylamino)phenyl, o-, m- or p-(N,N-diethylamino)phenyl, o-, m- or p-acetylphenyl, o-, m- or p-formylphenyl, o-, m- or p-fluorophenyl, o-, m- or p-bromophenyl, o-, m- or p-chlorophenyl or o-, m- or p-methylsulfonylphenyl.

Het is preferably, for example, 2- or 3-furyl, 2- or 3-thienyl, 1-, 2- or 3-pyrrolyl, 1-, 2-, 4- or 5-imidazolyl, 1-, 3-, 4- or 5-pyrazolyl, 2-, 4- or 5-oxazolyl, 3-, 4- or 5-isoxazolyl, 2-, 4- or 5-thiazolyl, 3-, 4- or 5-isothiazolyl, 2-, 3- or 4-pyridyl, 2-, 4-, 5- or 6-pyrimidinyl, furthermore preferably 1,2,3-triazol-1-, -4- or -5-yl, 1,2,4-

triazol-1-, -3- or -5-yl, 1- or 5-tetrazolyl, 1,2,3-oxadiazol-4- or -5-yl, 1,2,4-oxadiazol-3- or -5-yl, 1,3,4-thiadiazol-2- or -5-yl, 1,2,4-thiadiazol-3- or -5-yl, 1,2,3-thiadiazol-4- or -5-yl, 3- or 4-pyridazinyl, pyrazinyl, 1-, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 4- or 5-isoindolyl, 1-, 2-, 4- or 5-benzimidazolyl, 1-, 3-, 4-, 5-, 6- or 7-benzopyrazolyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 3-, 4-, 5-, 6- or 7-benzisoxazolyl, 2-, 4-, 5-, 6- or 7-benzothiazolyl, 2-, 4-, 5-, 6- or 7-benzisothiazolyl, 4-, 5-, 6- or 7-benz-2,1,3-oxadiazolyl, 2-, 3-, 4-, 5-, 6-, 7- or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 5-, 6-, 7- or 8-quinazolinyl, 5- or 6-quinoxalinyl, 2-, 3-, 5-, 6-, 7- or 8-2H-benzo[1,4]oxazinyl, furthermore preferably 1,3-benzodioxol-5-yl, 1,4-benzodioxan-6-yl, 2,1,3-benzothiadiazol-4- or -5-yl or 2,1,3-benzoxadiazol-5-yl.

The heterocyclic radicals may also be partially or fully hydrogenated.

Het may also be, for example, 2,3-dihydro-2-, -3-, -4- or -5-furyl, 2,5-dihydro-2-, -3-, -4- or -5-furyl, tetrahydro-2- or -3-furyl, 1,3-dioxolan-4-yl, tetrahydro-2- or -3-thienyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 2,5-dihydro-1-, -2-, -3-, -4- or -5-pyrrolyl, 1-, 2- or 3-pyrrolidinyl, tetrahydro-1-, -2- or -4-imidazolyl, 2,3-dihydro-1-, -2-, -3-, -4- or -5-pyrazolyl, tetrahydro-1-, -3- or -4-pyrazolyl, 1,4-dihydro-1-, -2-, -3- or -4-pyridyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5- or -6-pyridyl, 1-, 2-, 3- or 4-piperidinyl, 2-, 3- or 4-morpholinyl, tetrahydro-2-, -3- or -4-pyranyl, 1,4-dioxanyl, 1,3-dioxan-2-, -4- or -5-yl, hexahydro-1-, -3- or -4-pyridazinyl, hexahydro-1-, -2-, -4- or -5-pyrimidinyl, 1-, 2- or 3-piperazinyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-quinolyl, 1,2,3,4-tetrahydro-1-, -2-, -3-, -4-, -5-, -6-, -7- or -8-isoquinolyl, 2-, 3-, 5-, 6-, 7- or 8-3,4-dihydro-2H-benzo[1,4]oxazinyl, furthermore preferably 2,3-methylenedioxyphenyl, 3,4-

methylenedioxyphenyl, 2,3-ethylenedioxyphenyl, 3,4-ethylenedioxyphenyl, 3,4-(difluoromethylenedioxy)-phenyl, 2,3-dihydrobenzofuran-5- or -6-yl, 2,3-(2-oxo-methylenedioxy)phenyl or else 3,4-dihydro-2H-1,5-benzodioxepin-6- or -7-yl, furthermore preferably 2,3-dihydrobenzofuranyl or 2,3-dihydro-2-oxofuranyl.

Het is unsubstituted or mono- or polysubstituted by Hal, A, Ar', $COOR^5$, CN, $N(R^5)_2$, NO_2, Ar-$CONH-CH_2$.
"Poly" means di, tri, tetra or penta.
Het is very particularly preferably thiazole-2-, 4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl, 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen.

The compounds of the formula I may have one or more chiral centres and may therefore be present in various stereoisomeric forms. The formula I embraces all of these forms.

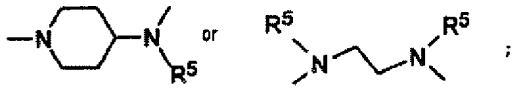
Consequently, the invention provides in particular those compounds of the formula I in which at least one of the abovementioned radicals has one of the preferred meanings given above. Some preferred groups of compounds can be expressed by the following moieties Ia to Ii which correspond to the formula I and where the radicals which are not defined more specifically have the meaning given for the formula I, but where

in Ia R^2 is H;

in Ib R^3 is R^5 or $-(CH_2)_m-COOR^5$;

in Ic R^4 is A, cycloalkyl, $-(CH_2)_nAr$ [sic], $-(CH_2)_mHet$ or $-CH=CH-Ar$;

in Id Y is O, NR^5, $N(CH_2)_m$-Ar, $N(CH_2)_m$-Het, $N(CH_2)_m$-$COOR^5$,



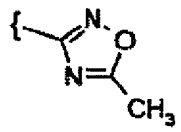
in Ie A is alkyl having 1-20 C atoms in which one or two CH_2 groups may be replaced by -CH=CH- groups and/or 1-7 H atoms may be replaced by F;

in If Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, phenyl, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOphenyl, $NHSO_2A$, $NHSO_2$phenyl, $COOR^5$, $CON(R^5)_2$, CONHphenyl, COR^5, COphenyl, $S(O)_nA$ or $S(O)_nAr$;

in Ig Ar' is phenyl;

in Ih Het is thiazol-2-, -4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl or 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen;

in Ii R^1 is $-C(=NH)-NH_2$, which can also be monosubstituted by -COA, $-CO-(CH_2)_m-Ar$, -COOA or OH,

or is  ,

R^2 is H,

R^3 is R^5 or $-(CH_2)_m-COOR^5$,

R^3 and X together are also -CO-N-, thus forming a 5-membered ring,

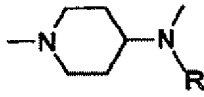
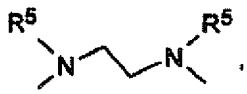
R^4 is A, cycloalkyl, $-(CH_2)_mAr$, $-(CH_2)_mHet$ or -CH=CH-Ar,

R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y is O, NR^5, $N(CH_2)_m-Ar$, $N(CH_2)_m-Het$,

$N(CH_2)_m-COOR^5$,  ,

 or  ,

NCH_2-CONH_2, $NCH_2-CONHA$, NCH_2-CONA_2, NCH_2-CONR^5Ar or $NCH_2-CONAr_2$,

W is a bond, $-SO_2-$, -CO-, -COO- or -CONH-,

A is alkyl having 1-20 C atoms in which one or two CH_2 groups may be replaced by -CH=CH- groups and/or 1-7 H atoms may be replaced by F,

Ar is phenyl which is unsubstituted or mono-, di- or trisubstituted by NH_2, OR^5, Hal, CN, alkyl having 1-10 carbon atoms, CF_3, CH_3SO_2, OCF_3, acetamido, $-C(=NH)-NH_2$, methoxycarbonyl or ethoxycarbonyl,

furthermore naphthyl which is monosubstituted by Hal, dimethylamino or methoxy and also unsubstituted biphenyl.

Het is thiazol-2-, -4- or -5-yl, thiophen-2- or -5-yl, chroman-6-yl, pyridin-2-, -3- or -4-yl, pyrimidin-2- or -5-yl, benzothiophen-2-yl, 1,3-benzodioxol-4- or -5-yl, 1,4-benzodioxan-5- or -6-yl, 2,1,3-benzothiadiazol-4- or -5-yl which is unsubstituted or mono- or polysubstituted by Hal, A, phenyl, OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOphenyl and/or carbonyl oxygen.

The compounds of the formula I and also the starting materials for their preparation are otherwise prepared by methods known per se, such as are described in the literature (for example in the standard works such as Houben-Weyl, Methoden der organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart), and in particular under the reaction conditions which are known and suitable for the reactions mentioned. In these reactions, variants which are known per se and are not mentioned here in more detail can also be utilized.

If desired, the starting materials can also be formed in situ, so that they are not isolated from the reaction mixture but are immediately reacted further to give the compounds of the formula I.

Compounds of the formula I can preferably be obtained by liberating the compounds of the formula I from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent.

Preferred starting materials for the solvolysis or hydrogenolysis are those which otherwise correspond to the formula I but, instead of one or more free amino

and/or hydroxyl groups, contain corresponding protected amino and/or hydroxyl groups, preferably those which, instead of an H atom which is bonded to an N atom, carry an amino-protective group, in particular those which, instead of an HN group, carry an R'-N group, in which R' is an amino-protective group, and/or those which, instead of the H atom of a hydroxyl group, carry a hydroxyl-protective group, for example those which correspond to the formula I but, instead of a -COOH group, carry a group -COOR", in which R" is a hydroxyl-protective group.

Preferred starting materials also include the oxadiazole derivatives which can be converted into the corresponding amidino compounds.

The introduction of the oxadiazole group is effected, for example, by reacting the cyano compounds with hydroxylamine and reaction with phosgene, dialkyl carbonate, chloroformic ester, N,N'-carbonyldiimidazole or acetic anhydride.

It is also possible for several - identical or different - protected amino and/or hydroxyl groups to be present in the molecule of the starting material. If the protective groups present differ from one another, in many cases they can be cleaved off selectively.

The term "amino-protective group" is generally known and relates to groups which are suitable for protecting (blocking) an amino group from chemical reactions but which can easily be removed after the desired chemical reaction has been carried out at other sites of the molecule. Typical such groups are, in particular, unsubstituted or substituted acyl, aryl, aralkoxymethyl or aralkyl groups. Since the amino-protective groups are removed after the desired reaction (or reaction sequence), their nature and size is otherwise not critical; however, those having 1-20, in particular 1-8

C atoms are preferred. The term "acyl group" is to be interpreted in the broadest sense in connection with the present process. It includes acyl groups derived from aliphatic, araliphatic, aromatic or heterocyclic carboxylic acids or sulfonic acids, and in particular alkoxycarbonyl, aryloxycarbonyl and, above all, aralkoxycarbonyl groups. Examples of such acyl groups are alkanoyl, such as acetyl, propionyl or butyryl; aralkanoyl, such as phenylacetyl; aroyl, such as benzoyl or toluyl; aryloxyalkanoyl, such as POA; alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, BOC (tert-butyloxycarbonyl), 2-iodoethoxycarbonyl; aralkyl-oxycarbonyl such as CBZ ("carbobenzoxy"), 4-methoxybenzyloxycarbonyl, FMOC; arylsulfonyl such as Mtr. Preferred amino-protective groups are BOC and Mtr, and furthermore CBZ, Fmoc, benzyl and acetyl.

The term "hydroxyl-protective group" is also generally known and relates to groups which are suitable for protecting a hydroxyl group from chemical reactions but which can easily be removed after the desired chemical reaction has been carried out at other sites of the molecule. Typical such groups are the abovementioned unsubstituted or substituted aryl, aralkyl or acyl groups, and furthermore also alkyl groups. The nature and the size of the hydroxyl-protective groups is not critical, since they are removed again after the desired chemical reaction or reaction sequence; groups having 1-20, in particular 1-10 C atoms are preferred. Examples of hydroxyl-protective groups are, inter alia, benzyl, p-nitrobenzoyl, p-toluenesulfonyl, tert-butyl and acetyl, benzyl and tert-butyl being particularly preferred.

The liberation of the compounds of the formula I from their functional derivatives is effected - depending on the protective group used - for example with strong acids, expediently with TFA or perchloric acid, but

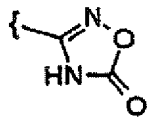
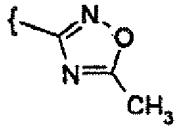
also with other strong inorganic acids, such as hydrochloric acid or sulfuric acid, strong organic carboxylic acids, such as trichloroacetic acid, or sulfonic acids, such as benzene- or p-toluenesulfonic acid. The presence of an additional inert solvent is possible but not always necessary. Suitable inert solvents are, preferably, organic solvents, for example carboxylic acids, such as acetic acid, ethers, such as tetrahydrofuran or dioxane, amides, such as DMF, halogenated hydrocarbons, such as dichloromethane, or furthermore also alcohols, such as methanol, ethanol or isopropanol, and water. Mixtures of the abovementioned solvents are furthermore possible. TFA is preferably used in excess without addition of a further solvent, and perchloric acid is used in the form of a mixture of acetic acid and 70% perchloric acid in a ratio of 9:1. The reaction temperatures for the cleavage are expediently between about 0 and about 50°, and the reaction is preferably carried out at between 15 and 30° (room temperature).

The groups BOC, OBut and Mtr can preferably be cleaved off, for example, with TFA in dichloromethane or with about 3 to 5N HCl in dioxane at 15-30°, and the FMOC group can be cleaved off with an approximately 5 to 50% solution of dimethylamine, diethylamine or piperidine in DMF at 15-30°.

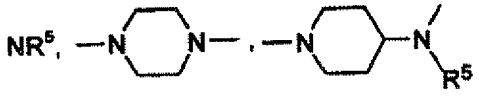
Protective groups which can be removed by hydrogenolysis (for example CBZ, benzyl or the liberation of the amidino group from its oxadiazole derivative) can be cleaved off, for example, by treatment with hydrogen in the presence of a catalyst (for example a noble metal catalyst, such as palladium, expediently on a support, such as carbon). Suitable solvents for this reaction are those mentioned above, in particular, for example, alcohols, such as methanol or ethanol, or amides, such as DMF. The hydrogenolysis is generally carried out at temperatures between about

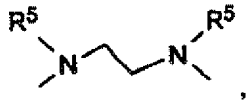
0 and 100° under pressures between about 1 and 200 bar, preferably at 20-30° and 1-10 bar. Hydrogenolysis of the CBZ group is effected readily, for example, on 5-10% Pd/C in methanol or with ammonium formate (instead of hydrogen) on Pd/C in methanol/DMF at 20-30°.

Compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  , or

 ,

W is $-SO_2-$ or -CO-,

and R^2 and R^4 are as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula II with compounds of the formula III.

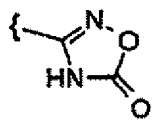
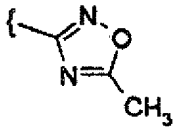
In the compounds of the formula III, L is preferably Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy), or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

The reaction is generally carried out in an inert solvent, in the presence of an acid binder, preferably an alkali metal hydroxide, carbonate or bicarbonate or an alkaline earth metal hydroxide, carbonate or bicarbonate, or of another salt of a weak acid of the alkali metals or alkaline earth metals, preferably of potassium, sodium, calcium or caesium. The addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of the amine component of the formula II or of the alkylation derivative of the formula III may also be favourable. Depending on the conditions used, the reaction time is between several minutes and 14 days, the reaction temperature is between approximately 0° and 150°, usually between 20° and 130°.

Suitable inert solvents are, for example, hydrocarbons, such as hexane, petroleum ether, benzene, toluene or xylene; chlorinated hydrocarbons, such as trichloroethylene, 1,2-dichloroethane, carbon tetrachloride, chloroform or dichloromethane; alcohols, such as methanol, ethanol, isopropanol, n-propanol, n-butanol or tert-butanol; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran (THF) or dioxane; glycol ethers, such as ethylene glycol monomethyl or monoethyl ether (methylglycol or ethylglycol) or ethylene glycol dimethyl ether (diglyme); ketones, such as acetone or butanone; amides, such as acetamide, dimethylacetamide, N-methylpyrrolidone (NMP) or dimethylformamide (DMF); nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide (DMSO); carbon disulfide; carboxylic acids, such as formic acid or acetic acid; nitro compounds, such as nitromethane or nitrobenzene; esters, such as ethyl acetate, or mixtures of the solvents mentioned.

The starting materials of the formulae II and III are generally known. Those which are novel, however, can be prepared by methods known per se.

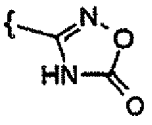
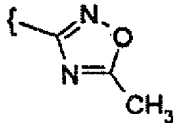
Compounds of the formula I

in which R^1 is  or  ,

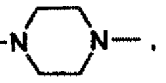
R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
W is a bond,
and R^2 and R^4 are as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula II in which Y is O with compounds of the formula IV in a Mitsunobu reaction in the presence of, for example, triphenylphosphine and diethylazo dicarboxylate in an inert solvent.

The starting materials of the formula II in which Y is O, and those of the formula IV, are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

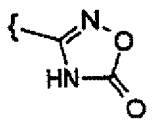
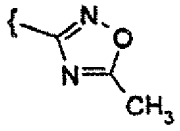
W is a bond,
R^4 is $-[C(R^5)_2]_m Ar$ or $-[C(R^5)_2]_m Het$,
n [sic] is 0
and R^2 is as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula V with compounds of the formula VI.

In the compounds of the formula V L is preferably Cl, Br, I or a reactively modified OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy), or arylsulfonyloxy having 6-10 C atoms (preferably phenyl- or p-tolylsulfonyloxy).

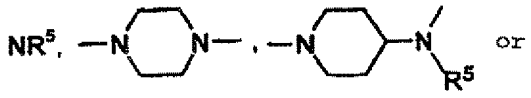
The reaction of the compounds of the formula V with compounds of the formula VI is preferably carried out in an inert solvent and at temperatures as indicated above.

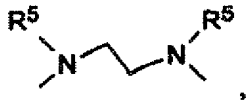
The starting materials of the formulae V and VI are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

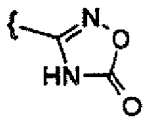
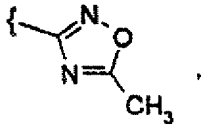
in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

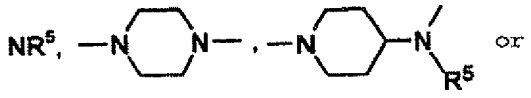
Y is  or



W is -CONH-,
and R^2 and R^4 are as defined in Claim 1,
can preferably be obtained by reacting compounds of the formula II

in which R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

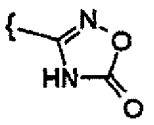
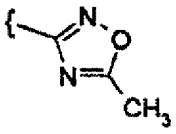
Y is  or

W is -CONH-,
and R^2 and R^5 are as defined in Claim 1,
with compounds of the formula VII.

The reaction of these compounds of the formula II in which W is -CONH- with compounds of the formula VII is preferably carried out in an inert solvent and at temperatures as indicated above.

The starting materials of the formula II in which W is -CONH- and of the formula VII are generally known. Those which are novel, however, can be prepared by methods known per se.

Compounds of the formula I

in which R^1 is  or  ,

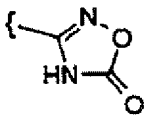
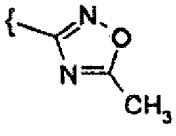
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

W is SO_2,

and R^2 and R^4 are as defined in Claim 1 can preferably be obtained by reacting compounds of the formula II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$

and R^2 and R^5 are as defined in Claim 1, with compounds of the formula VIII.

In the compounds of the formula VIII, L is preferably Cl, Br, I or a reactively derivatized OH group, such as, for example, an activated ester, an imidazolide or alkylsulfonyloxy having 1-6 C atoms (preferably methylsulfonyloxy) or arylsulfonyloxy having 6-10 C atoms (preferably phenyl or p-tolylsulfonyloxy).

The reaction of the compounds of the formula II in which Y is $N[C(R^5)_2]_m$-$COOR^5$ with compounds of the

formula VIII is preferably carried out in an inert solvent and at the temperatures given above.

Compounds of the formula I in which
X is NH and
R^3 is H
and R^1, R^2, R^4, Y and W are as defined in Claim 1, can be liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolyzing agent. This is carried out under conditions like those described under "protective group removal".

Compounds of the formula I in which R^1 is $-C(=NH)-NH_2$ can furthermore be obtained from the corresponding cyano compound.
The conversion of a cyano group into an amidino group is carried out by reaction with, for example, hydroxylamine and subsequent reduction of the N-hydroxamidine with hydrogen in the presence of a catalyst, such as, for example, Pd/C.
To prepare an amidine of the formula I (R^1 = $-C(=NH)-NH_2$), ammonia can also be added onto a nitrile of the formula I (R^1 = CN). The addition is preferably carried out in several stages by a procedure in which, in a manner known per se, a) the nitrile is converted with H_2S into a thioamide, which is converted with an alkylating agent, for example CH_3I, into the corresponding S-alkyl-imidothioester, which in turn reacts with NH_3 to give the amidine, b) the nitrile is converted with an alcohol, for example ethanol, in the presence of HCl into the corresponding imidoester, and this is treated with ammonia, or c) the nitrile is reacted with lithium bis(trimethylsilyl)amide and the product is then hydrolysed.

Furthermore, it is possible to convert a compound of the formula I into another compound of the formula I by converting one or more radicals Y, R^1, R^2, R^3 and/or R^4 into one or more radicals Y, R^1, R^2, R^3 and/or R^4, for

example by acylating an amino group or reducing nitro groups (for example by hydrogenation over Raney nickel or Pd/carbon in an inert solvent, such as methanol or ethanol) to amino groups.

Esters can be hydrolysed, for example with acetic acid or with NaOH or KOH in water, water-THF or water-dioxane at temperatures between 0 and 100°.

It is furthermore possible to acylate free amino groups in a customary manner with an acyl chloride or acid anhydride or to alkylate with an unsubstituted or substituted alkyl halide, expediently in an inert solvent, such as dichloromethane or THF, and/or in the presence of a base, such as triethylamine or pyridine, at temperatures between -60 and +30°.

A base of the formula I can be converted into the associated acid addition salt with an acid, for example by reaction of equivalent amounts of the base and the acid in an inert solvent, such as ethanol, and subsequent evaporation. Acids which give physiologically acceptable salts are particularly suitable for this reaction. Thus, it is possible to use inorganic acids, for example sulfuric acid, nitric acid, hydrohalic acids, such as hydrochloric acid or hydrobromic acid, phosphoric acids, such as orthophosphoric acid, sulfaminic acid, or furthermore organic acids, in particular aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, for example formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, lactic acid, tartaric acid, malic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid,

naphthalene-mono- or -disulfonic acids and laurylsulfuric acid. Salts with physiologically unacceptable acids, for example picrates, can be used for isolation and/or purification of the compounds of the formula I.

On the other hand, compounds of the formula I can be converted with bases (for example sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate) into the corresponding metal, in particular alkali metal or alkaline earth metal salts or into the corresponding ammonium salts.
It is also possible to use physiologically acceptable organic bases, such as, for example, ethanolamine.

Owing to their molecular structure, the compounds of the formula I according to the invention can be chiral and can consequently be present in various enantiomeric forms. They may therefore be present in racemic or in optically active form.

Since the pharmaceutical activity of the racemates and/or the stereoisomers of the compounds according to the invention may differ, it may be desirable to use the enantiomers. In these cases, the end product or even the intermediates may be separated into enantiomeric compounds using chemical or physical means known to the person skilled in the art, or they may even be employed as such in the synthesis.

In the case of racemic amines, diastereomers are formed from the mixture by reaction with an optically active separating agent. Suitable separating agents are, for example, optically active acids, such as the R- and S-forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, suitable N-protected amino acids (for example N-benzoylproline or N-benzenesulfonylproline) or the various optically active camphorsulfonic acids. A chromatographic separation of the enantiomers can

also be advantageously carried out with the aid of an optically active separating agent (for example dinitrobenzoylphenylglycine, cellulose triacetate or other carbohydrate derivatives or chiral derivatized methacrylate polymers immobilized on silica gel). Solvents which are suitable for this purpose are aqueous or alcoholic solvent mixtures, such as, for example, hexane/isopropanol/acetonitrile, for example in the ratio 82:15:3.

The invention furthermore provides the use of the compounds of the formula I and/or their physiologically acceptable salts for the preparation of pharmaceutical formulations, in particular by a non-chemical route. For this purpose, they can be brought into a suitable dosage form together with at least one solid, liquid and/or semi-liquid carrier or auxiliary, and if appropriate in combination with one or more further active compounds.

The invention furthermore provides pharmaceutical formulations comprising at least one compound of the formula I and/or one of its physiologically acceptable salts.

These formulations can be used as medicaments in human or veterinary medicine. Possible carriers are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatine, carbohydrates, such as lactose or starch, magnesium stearate, talc and petroleum jelly. Tablets, pills, coated tablets, capsules, powders, granules, syrups, juices or drops are used, in particular, for oral administration, suppositories are used for rectal administration, solutions, preferably oily or aqueous solutions, and

furthermore suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical administration. The novel compounds can also be lyophilized and the resulting lyophilisates can be used, for example, for the preparation of injection formulations. The formulations mentioned can be sterilized and/or comprise auxiliaries, such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for influencing the osmotic pressure, buffer substances, dyestuffs, flavourings and/or several further active compounds, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be employed for combating and preventing thromboembolic disorders, such as thrombosis, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

For this purpose, the substances according to the invention are usually preferably administered in dosages of between about 1 and 500 mg, in particular between 5 and 100 mg per dosage unit. The daily dosage is preferably between about 0.02 and 10 mg/kg of body weight. However, the specific dose for each patient depends on the most diverse factors, for example on the activity of the specific compound employed, on the age, body weight, general state of health, sex, diet, on the administration time and route, and on the rate of excretion, medicament combination and severity of the particular disease to which the therapy applies. Oral administration is preferred.

All temperatures hereinabove and hereinbelow are given in °C. In the following examples, "customary work-up" means: water is added, if necessary, the pH is brought to values of between 2 and 10, if necessary, depending

on the structure of the end product, the mixture is extracted with ethyl acetate or dichloromethane, the organic phase is separated off, dried over sodium sulfate and evaporated and the residue is purified by chromatography over silica gel and/or crystallization. Rf values are for silica gel; mobile phase: ethyl acetate/methanol 9:1.

Mass spectrometry (MS):
EI (electron impact ionization) M^+
FAB (fast atom bombardment) $(M+H)^+$

Example 1

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyl-oxazolidin-2-one ("A") [obtainable by reaction of 3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenyl]-2-oxoxazolidin-5-ylmethyl methanesulphonate with 1-tert-butoxycarbonylpiperazine and sodium bicarbonate in acetonitrile; removal of the BOC group with HCl/dioxane and subsequent treatment with sodium hydroxide solution] and 110 mg of 2,4,6-trichlorobenzenesulphonyl chloride in 10 ml of dichloromethane is admixed with 400 mg of 4-dimethylaminopyridine on polystyrene and stirred at room temperature for 18 hours. The mixture is filtered and the solvent is removed, giving 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]5-[4-(24,6-trichlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one, FAB 586/588.

Similarly, reaction of "A"

with 4-biphenylylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-phenylvinylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-phenylvinylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-nitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,5-dimethoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,5-dimethoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-naphthylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-chloro-4-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-chloro-4-fluorophenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with (2-acetamido-4-methylthiazol-5-yl)sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((2-acetamido-4-methylthiazol-5-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-cyanophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-cyanophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 5-nitro-2-methylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(5-nitro-2-methylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with benzylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-benzylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with decylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-decylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 2-trifluoromethylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-trifluoromethylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 3-chloro-4-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-chloro-4-fluorophenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 4-chloro-2,5-dimethylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chloro-2,5-dimethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-fluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-fluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3,4-dibromophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dibromophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-chlorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-chlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,6-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,6-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,4-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,5-dichlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dichlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-naphthylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with methylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-methylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 2-methylsulfonylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-methylsulfonylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2-nitrobenzylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitrobenzylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethoxyphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with (1S)-(camphor-10-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(((1S)camphor-10-yl)sulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (1R)-(camphor-10-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(((1R)camphor-10-yl)sulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with (2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-isopropylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-isopropylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-tert-butylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tert-butylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-butylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,5-dinitro-4-methoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dinitro-4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with ethylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-ethylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 4-nitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-nitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-trifluoromethoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2,4-dinitrophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4-dinitrophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with isopropylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-isopropylsulfonylpiperazin-1-ylmethyl)oxazolidin-2-one;

with 4-ethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-ethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-bromo-2-trifluoromethoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-bromo-2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2,3,4-trifluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,3,4-trifluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3,4-difluorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2,2,2-trifluoroethylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,2,2-trifluoroethylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 3-nitro-4-methylphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-nitro-4-methylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2-nitro-6-chlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitro-6-chlorophenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 2,5-dimethoxyphenylacetyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,5-dimethoxyphenylacetyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3,4-dichlorobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-dichlorobenzoyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-fluorobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-fluorobenzoyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-trifluoromethoxybenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxybenzoyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 3-pyridylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-pyridylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 2-benzothienylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-benzothienylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-chlorophenylacetyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chlorophenylacetyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 1-naphthylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with (1,3-benzodioxol-5-yl)carbonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-((1,3-benzodioxol-5-yl)carbonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 3-nitrobenzoyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-nitrobenzoyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-biphenylylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;
with cyclopentylcarbonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclopentylcarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with [5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl]-sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl)sulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 4-chlorophenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-chlorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl-sulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octyl-sulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-butoxy-5-(1,1-dimethylpropyl)phenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-butoxy-5-(1,1-dimethylpropyl)phenylsulfonyl]-piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenyl-sulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenyl-sulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 2-nitro-4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-nitro-4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-bromo-2-ethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-bromo-2-ethylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 4-trifluoromethylphenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-yl-methyl]oxazolidin-2-one;

with 3,4-difluorophenylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 1-naphthylsulfonyl chloride gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-methoxyphenylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-tolylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tolylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 4-propylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-propylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one;

with 6-chloro-2-naphthylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 2-(naphth-1-yl)ethylsulfonyl chloride gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with isobutyl chloroformate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-isobutyloxycarbonyl)piperazin-1-ylmethyl]oxazolidin-2-one.

Example 2

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4,6-trichlorophenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one in 15 ml of methanol is admixed with 100 mg of Raney nickel and a drop of acetic acid and hydrogenated at room temperature for 8 hours. The catalyst is filtered off and the solvent is removed. This gives 4-(2-oxo-5-[4-

(2,4,6-trichlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 546/548.

Similarly, the benzamidine derivatives below are obtained from the compounds obtained in Example 1 by hydrogenation

4-{2-oxo-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 520;

4-{2-oxo-5-[4-(2-phenylethylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 472;

4-{2-oxo-5-[4-(2-aminophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 459;

4-{2-oxo-5-[4-(2,5-dimethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 504;

4-{2-oxo-5-[4-(2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 494;

4-{2-oxo-5-[4-(2-chloro-4-fluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 496;

4-{2-oxo-5-[4-((2-acetamido-4-methylthiazol-5-yl)-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 522;

4-{2-oxo-5-[4-(2-cyanophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 469;

4-{2-oxo-5-[4-(5-amino-2-methylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 473;

4-{2-oxo-5-(4-benzylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 458;

4-{2-oxo-5-(4-decylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 508;

4-{2-oxo-5-[4-(2-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3-chloro-4-fluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 496;

4-{2-oxo-5-[4-(4-chloro-2,5-dimethylphenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 506;

4-{2-oxo-5-[4-(2-fluorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 462;

4-{2-oxo-5-[4-(3,4-dibromophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 600/602/604;

4-{2-oxo-5-[4-(3-chlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 478;

4-{2-oxo-5-[4-(2,6-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3,4-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 512;

4-{2-oxo-5-[4-(3,5-dichlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(2-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{2-oxo-5-(4-methylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 382;

4-{2-oxo-5-[4-(2-methylsulfonylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 522;

4-{2-oxo-5-[4-(2-aminobenzylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 473;

4-{2-oxo-5-[4-((4-methoxycarbonyl-3-methoxythiophen-2-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 538;

4-{2-oxo-5-[4-(3-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(4-trifluoromethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 528;

4-{2-oxo-5-[4-(((1S)-camphor-10-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{2-oxo-5-[4-(((1R)-camphor-10-yl)sulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{2-oxo-5-[4-((2,2,5,7,8-pentamethylchroman-6-yl)sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, acetate, FAB 570;

4-{2-oxo-5-[4-(4-isopropylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 486;

4-{2-oxo-5-[4-(4-tert-butylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate;

4-{2-oxo-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 500;

4-{2-oxo-5-[4-(3,5-diamino-4-methoxyphenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, acetate, FAB 504;

4-{2-oxo-5-(4-ethylsulfonylpiperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine, acetate, FAB 396;

4-{2-oxo-5-[4-(4-nitrophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 459;

4-{2-oxo-5-[4-(2-trifluoromethoxyphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 528;

4-{2-oxo-5-[4-(2,4-diaminophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 474;

4-{2-oxo-5-(4-isopropylsulfonylpiperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 410;

4-{2-oxo-5-[4-(4-ethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 472;

4-{2-oxo-5-[4-(4-bromo-2-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}-benzamidine, acetate, FAB 606/608;

4-{2-oxo-5-[4-(2,3,4-trifluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 498;

4-{2-oxo-5-[4-(3,4-difluorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 480;

4-{2-oxo-5-[4-(2,2,2-trifluoroethylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 450;

4-{2-oxo-5-[4-(3-amino-4-methylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 473;

4-{2-oxo-5-[4-(2-amino-6-chlorophenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 585;

4-{2-oxo-5-[4-(2,5-dimethoxyphenylacetyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 482;

4-{2-oxo-5-[4-(3,4-dichlorobenzoyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 476;

4-{2-oxo-5-[4-(3-fluorobenzoyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 426;

4-{2-oxo-5-[4-(4-trifluoromethoxybenzoyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 492;

4-{2-oxo-5-[4-(3-pyridylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 409;

4-{2-oxo-5-[4-(2-benzothienylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 463;

4-{2-oxo-5-[4-(4-chlorophenylacetyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 456;

4-{2-oxo-5-[4-(1-naphthylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{2-oxo-5-[4-((1,3-benzodioxol-5-yl)carbonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 452;

4-{2-oxo-5-[4-(3-aminobenzoyl)piperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine, acetate, FAB 423;

4-{2-oxo-5-[4-(4-biphenylylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 484;

4-{2-oxo-5-[4-(cyclopentylcarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 400;

4-{2-oxo-5-{4-[5-chloro-1-(4-methylphenyl)-1H-pyrazol-4-yl)sulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 558;

4-{2-oxo-5-[4-(4-chlorophenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 478;

4-{2-oxo-5-{4-[5,7,7-trimethyl-2-(1,3,3-trimethylbutyl)octylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 620;

4-{2-oxo-5-{4-[2-butoxy-5-(1,1-dimethylpropyl)-phenylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 586;

4-{2-oxo-5-{4-[2-butoxy-5-(1,1,3,3-tetramethylbutyl)phenylsulfonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 628;

4-{2-oxo-5-[4-(2-amino-4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate;

4-{2-oxo-5-[4-(4-bromo-2-ethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 550/552;

4-{2-oxo-5-[4-(4-trifluoromethylphenylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512;

4-{2-oxo-5-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 528;

4-{2-oxo-5-[4-(isobutyloxycarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 404.

Similarly, reaction of 3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 6-chloro-2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

3-{2-oxo-5-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, m.p. 118°C.

Similarly, reaction of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 6-methoxy-2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

4-{2-oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)-piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine.

Similarly, reaction of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-piperazin-1-ylmethyloxazolidin-2-one with 2-fluorobenzyl chloride and subsequent hydrogenation gives the compound

4-{2-oxo-5-[4-(2-fluorobenzyl)piperazin-1-yl-methyl]oxazolidin-3-yl}benzamidine.

Example 3

A solution of 100 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2,4,6-trichlorophenyl-sulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one in 8 ml of methanol is admixed with 3 ml of 1N aqueous sodium hydroxide solution and stirred at 60° for 48 hours. This gives, after customary work-up, 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol, FAB 556/558.

Similarly,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,4-difluorophenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(3-fluoro-4-methoxyphenylsulfonyl)-piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(1-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenylamino]-1-[4-(1-naphthylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(4-trifluoromethylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-biphenylylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(4-biphenylylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(3-trifluoromethylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)phenylamino]-1-[4-(4-trifluoromethoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-isopropylphenylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-isopropylphenylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-butylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-butylphenylsulfonyl)piperazin-1-yl]propanol-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-methoxyphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-methoxyphenylsulfonyl)piperazin-1-yl]-propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-tolylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-tolylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(4-propylphenylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl-amino]-1-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(2-phenylvinylsulfonyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2-phenylvinylsulfonyl)piperazin-1-yl]propan-2-ol;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-yl}propan-2-ol.

Similarly, 4-{2-oxo-5-[4-(6-methoxy-2-naphthylsulfonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine gives the compound

4-{2-hydroxy-3-[4-(6-methoxynaphthalene-2-sulfonyl)piperazin-1-yl]propylamino}benzamidine, diacetate, FAB 498 and

4-{2-oxo-5-[4-(2-fluorobenzyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine gives the compound

4-{2-hydroxy-3-[4-(2-fluorobenzyl)piperazin-1-yl]propylamino}benzamidine, acetate, FAB 386.

Example 4

A solution of 60 mg of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenylamino]-1-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]propan-2-ol in 5 ml of methanol is admixed with 50 mg of Raney nickel and a drop of acetic acid and hydrogenated at room

temperature for 8 hours. The catalyst is filtered off and the solvent is removed. This gives 4-{3-[4-(2,6-dichloro-4-methoxyphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 516/518.

Similarly, the compounds below are obtained from the propan-2-ol derivatives listed under Example 3 by hydrogenation

4-{3-[4-(3-fluoro-4-methoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 466;

4-{3-[4-(1-naphthylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 468;

4-{3-[4-(4-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 486;

4-{3-[4-(4-biphenylylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 494;

4-{3-[4-(3-trifluoromethylphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 486;

4-{3-[4-(4-trifluoromethoxyphenylsulfonyl)-piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 502;

4-{3-[4-(4-isopropylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 460;

4-{3-[4-(4-butylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 474;

4-{3-[4-(4-methoxyphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 448;

4-{3-[4-(4-tolylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 432;

4-{3-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 460;

4-{3-[4-(6-chloro-2-naphthylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 502;

4-{3-[4-(2-phenylvinylsulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine, acetate, FAB 446;

4-{3-{4-[2-(naphth-1-yl)ethylsulfonyl]piperazin-1-yl}-2-hydroxypropylamino}benzamidine, acetate, FAB 496.

Example 5

A solution of 10.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate, 6.73 g of 4-BOC-aminopiperidine and 8.5 g of sodium bicarbonate in 200 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up

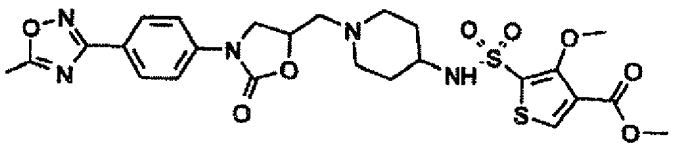
gives 5-(4-BOC-aminopiperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one.

The BOC group is cleaved off using TFA in dichloromethane, giving 5-(4-aminopiperidin-1-ylmethyl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-oxazolidin-2-one ("B").

Similarly to Example 1, reaction of "B"

with (3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonyl chloride gives

N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-(3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonamide



;

with benzenesulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-benzenesulfonamide;

with 3,4-dimethoxybenzenesulfonyl chloride gives
3,4-dimethoxy-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with butylsulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-butylsulfonamide;

with 2,4,6-trimethylbenzenesulfonyl chloride gives
2,4,6-trimethyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
phenylvinyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)sulfonamide;

with 2-methylsulfonylbenzenesulfonyl chloride gives
2-methylsulfonyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)benzenesulfonamide;

with 4-biphenylylsulfonyl chloride gives

4-biphenylyl-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)sulfonamide;

with 5-dimethylamino-1-naphthylsulfonyl chloride gives
5-dimethylamino-N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-piperidin-4-yl)-1-naphthylsulfonamide;

with 1-naphthylsulfonyl chloride gives
N-(1-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}piperidin-4-yl)-1-naphthylsulfonamide.

By hydrogenation similarly to Example 2, these give the compounds below

4-{5-[4-((3-methoxy-4-methoxycarbonylthiophen-2-yl)sulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 552;

4-{5-[4-(benzenesulfonylamino)piperidin-1-yl-methyl}-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 458;

4-{5-[4-(3,4-dimethoxybenzenesulfonyl-amino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 518;

4-{5-[4-(butylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 438;

4-{5-[4-(2,4,6-trimethylbenzenesulfonylamino)-piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 500;

4-{5-[4-(phenylethylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 486;

4-{5-[4-(2-methylsulfonylbenzenesulfonylamino)-piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 536;

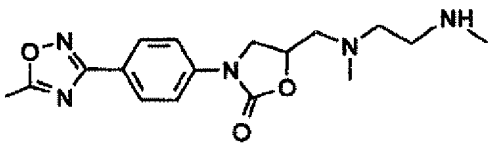
4-{5-[4-(4-biphenylylsulfonylamino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 533;

4-{5-[4-(5-dimethylamino-1-naphthylsulfonyl-amino)piperidin-1-ylmethyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 551;

4-{5-[4-(1-naphthylsulfonylamino)piperidin-1-yl-methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 458.

Example 6

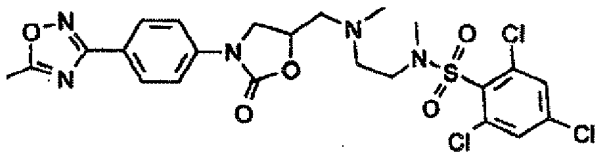
A solution of 10.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methane-sulfonate, 7.4 g of N,N'-dimethylethylenediamine and 8.5 g of sodium bicarbonate in 400 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up gives 5-{[methyl-(2-methylaminoethyl)amino]methyl}-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("C").



"C"

Similarly to Example 1, reaction of "C"

with 2,4,6-trichlorophenylsulfonyl chloride gives 2,4,6-trichloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide



with 2-trifluoromethoxyphenylsulfonyl chloride gives
2-trifluoromethoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 2,4,6-trichlorophenylsulfonyl chloride gives
2,4,6-trichloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-trifluoromethylphenylsulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-isopropylphenylsulfonyl chloride gives
4-isopropyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-propylphenylsulfonyl chloride gives
4-propyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-acetamidophenylsulfonyl chloride gives
4-acetamido-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 2-naphthylsulfonyl chloride gives

N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-2-naphthylsulfonamide;

with 3-trifluoromethylphenylsulfonyl chloride gives
3-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-chloro-3-nitrophenylsulfonyl chloride gives
4-chloro-3-nitro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]phenylvinylsulfonamide;

with benzylsulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzylsulfonamide;

with tolylsulfonyl chloride gives
4-methyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-methoxyphenylsulfonyl chloride gives
4-methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 1-naphthylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-1-naphthylsulfonamide;

with 4-biphenylylsulfonyl chloride gives
N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-4-biphenylylsulfonamide;

with 3,4-difluorophenylsulfonyl chloride gives
3,4-difluoro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-pentylphenylsulfonyl chloride gives
4-pentyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

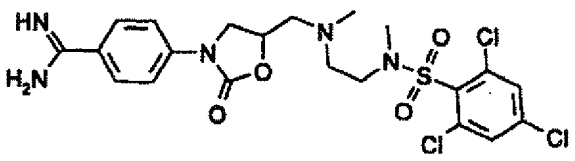
with 4-butylphenylsulfonyl chloride gives
4-butyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 4-methylsulfonylphenylsulfonyl chloride gives
4-methylsulfonyl-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]benzenesulfonamide;

with 6-chloro-2-naphthylsulfonyl chloride gives
6-chloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino)ethyl]-2-naphthylsulfonamide;

By hydrogenation similarly to Example 2, these give the compounds below

4-{5-[(methyl-{2-[methyl-(2,4,6-trichlorobenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 548/550



;

4-{5-[(methyl-{2-[methyl-(2-trifluoromethoxy-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine, acetate, FAB 530;

4-{5-[(methyl-{2-[methyl-(4-trifluoromethyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 514;

4-{5-[(methyl-{2-[methyl-(4-isopropylbenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 488;

4-{5-[(methyl-{2-[methyl-(4-propylbenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 488;

4-{5-[(methyl-{2-[methyl-(4-acetamidobenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 503;

4-{5-[(methyl-{2-[methyl-(2-naphthylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, acetate, FAB 496;

4-{5-[(methyl-{2-[methyl-(3-trifluoromethyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 514;

4-{5-[(methyl-{2-[methyl-(3-amino-4-chlorobenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 495;

4-{5-[(methyl-{2-[methyl(phenylethylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 474;

4-{5-[(methyl-{2-[methyl(benzylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 460;

4-{5-[(methyl-{2-[methyl-(4-tolylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 460;

4-{5-[(methyl-{2-[methyl-(4-methoxybenzene-sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 476;

4-{5-[(methyl-{2-[methyl-(1-naphthylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 496;

4-{5-[(methyl-{2-[methyl-(4-biphenylylsulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine, trifluoroacetate, FAB 522;

4-{5-[(methyl-{2-[methyl-(3,4-difluorobenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 516;

4-{5-[(methyl-{2-[methyl-(4-pentylbenzene sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 516;

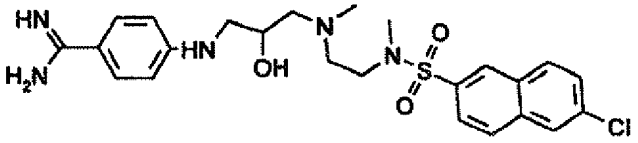
4-{5-[(methyl-{2-[methyl-(4-butylbenzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 502;

4-{5-[(methyl-{2-[methyl-(4-methylsulfonyl-benzenesulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 502;

4-{5-[(methyl-{2-[methyl-(6-chloro-2-naphthyl sulfonyl)amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, trifluoroacetate, FAB 530.

Similarly to Examples 3 and 4, 6-chloro-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-amino)ethyl]-2-naphthylsulfonamide gives the compound

4-[3-({2-[(6-chloro-2-naphthylsulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]-benzamidine, acetate, FAB 504



and 7-methoxy-N-methyl-N-[2-(methyl-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl-methyl}amino)ethyl]-2-naphthylsulfonamide gives the compound

4-[3-({2-[(7-methoxy-2-naphthylsulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]benz-amidine, acetate, FAB 500.

Similar to Example 3, cleavage of the oxazolidinone ring of

4-{5-[(methyl-{2-[methyl-(4-biphenylylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine,

4-{5-[(methyl-{2-[methyl-(4-isopropylbenzenesulfonyl)-amino]ethyl}amino)methyl]-2-oxooxazolidin-3-yl}-benzamidine,

4-{5-[(methyl-{2-[methyl-(1-naphthylsulfonyl)amino]-ethyl}amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, give

the compounds below

4-[3-({2-[(4-biphenylylsulfonyl)methylamino]-ethyl}methylamino)-2-hydroxypropylamino]benzamidine, diacetate, EI 460 ($M^+ - NH_2$);

4-[3-({2-[(4-isopropylbenzenesulfonyl)methyl-amino]ethyl}methylamino)-2-hydroxypropylamino]-benzamidine, diacetate, EI 461;

4-[3-({2-[(1-naphthylsulfonyl)methylamino]ethyl}-methylamino)-2-hydroxypropylamino]benzamidine, diacetate, EI 469.

Example 7

A solution of 10.6 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methane-sulfonate and 3.17 g of sodium azide in 50 ml of acetonitrile is heated under reflux for 40 hours. Customary work-up gives 5-azidomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one.
7.7 g of azido compound are suspended in ethylene glycol dimethyl ether, 3.6 ml of trimethyl phosphite are then added and the mixture is stirred under reflux for 1.5 hours. 4.9 ml of half-concentrated HCl are added and the mixture is boiled for a further 3 hours. Customary work-up gives 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one, hydrochloride.

The compound is suspended in dichloromethane, admixed with basic ion exchanger and stirred for 2 hours. Removal of the ion exchanger and the solvent gives 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]oxazolidin-2-one ("D").

Similarly to Example 1, reaction of "D"

with 3,4-difluorobenzenesulfonyl chloride gives
3,4-difluoro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzene-sulfonamide;

with 4-methoxybenzenesulfonyl chloride gives
4-methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfon-amide;

with 4-chloro-3-nitrobenzenesulfonyl chloride gives
4-chloro-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with butylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}butylsulfonamide;

with 3-trifluoromethylbenzenesulfonyl chloride gives
3-trifluoromethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 2-naphthylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide.

Similarly to Example 2, the compounds below are obtained by hydrogenation of the sulfonamides

The compound is suspended in dichloromethane, admixed with basic ion exchanger and stirred for 2 hours. Removal of the ion exchanger and the solvent gives 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]oxazolidin-2-one ("D").

Similarly to Example 1, reaction of "D"

with 3,4-difluorobenzenesulfonyl chloride gives
3,4-difluoro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzene-sulfonamide;

with 4-methoxybenzenesulfonyl chloride gives
4-methoxy-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfon-amide;

with 4-chloro-3-nitrobenzenesulfonyl chloride gives
4-chloro-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with butylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}butylsulfonamide;

with 3-trifluoromethylbenzenesulfonyl chloride gives
3-trifluoromethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 2-naphthylsulfonyl chloride gives
N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide.

Similarly to Example 2, the compounds below are obtained by hydrogenation of the sulfonamides

4-[3-(4-methoxybenzenesulfonylamino)-2-hydroxypropylamino]benzamidine;

4-chloro-3-nitro-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-[3-(3-amino-4-chlorobenzenesulfonylamino)-2-hydroxypropylamino]benzamidine;

N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide gives
4-[3-(butylsulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 329;

3-trifluoromethyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-[3-(3-trifluoromethylbenzenesulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 417;

N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-propylsulfonamide gives
4-[3-(propylsulfonylamino)-2-hydroxypropylamino]benzamidine, acetate, FAB 391.

Example 9

A solution of 30.0 g of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate and 300 ml of aqueous methylamine solution in 300 ml of THF is heated under pressure at 80°C for 18 hours. Customary work-up gives 5-methylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("E").

Similarly to Example 1, reaction of "E"

with butylsulfonyl chloride gives

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide;

with 4-isopropylbenzenesulfonyl chloride gives
4-isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 3-trifluoromethylbenzenesulfonyl chloride gives
3-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with phenylvinylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}phenylvinylsulfonamide;

with 2-naphthylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide;

with 4-propylbenzenesulfonyl chloride gives
4-propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 4-methoxybenzenesulfonyl chloride gives
4-methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl}-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 2,4,6-trimethylbenzenesulfonyl chloride gives
2,4,6-trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with benzoyl chloride gives

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzamide;

with 2-naphthylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthyl-carboxamide;

with cyclohexylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}cyclohexyl-carboxamide;

with 4-biphenylylcarbonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylyl-carboxamide;

with 4-chlorobenzoyl chloride gives
4-chloro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzamide;

with 4-(1,1-dimethylpropyl)benzenesulfonyl chloride gives
4-(1,1-dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with 3,4-difluorobenzenesulfonyl chloride gives
3,4-difluoro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 4-tert-butylbenzenesulfonyl chloride gives
4-tert-butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

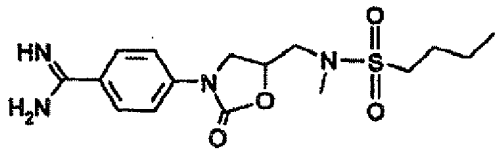
with 4-trifluoromethylbenzenesulfonyl chloride gives
4-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide;

with 4-pentylbenzenesulfonyl chloride gives
4-pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide;

with 1-naphthylsulfonyl chloride gives
N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl]-1-naphthylsulfonamide.

Similarly to Example 2, the compounds below are obtained

5-{5-[((butylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 369



;

5-{5-[((4-isopropylbenzenesulfonyl)methylamino)-methyl}-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 431;

5-{5-[((3-trifluoromethylbenzenesulfonyl)methyl-amino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 457;

5-{5-[((phenylethylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine, acetate, FAB 417;

5-{5-[((2-naphthylsulfonyl)methylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((4-propylbenzenesulfonyl)methylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((4-methoxybenzenesulfonyl)methylamino)-methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[((2,4,6-trimethylbenzenesulfonyl)methyl-amino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(benzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(2-naphthylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(cyclohexylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(4-biphenylylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine;

5-{5-[(4-chlorobenzoylmethylamino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine.

Similarly, methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate and butylamine give the compound 5-butylaminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]oxazolidin-2-one ("E-1")

Reaction of "E-1"

with 6-chloro-2-naphthylsulfonyl chloride gives

6-chloro-N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide;

with 4-biphenylylsulfonyl chloride gives

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylyl-sulfonamide;

with 2-naphthylsulfonyl chloride gives

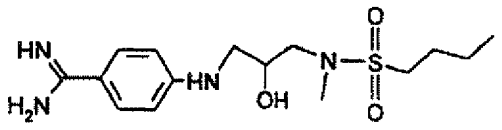
N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfon-amide.

Example 10

Similarly to Examples 3 and 4,

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}butylsulfonamide gives

4-{3-[(butane-1-sulfonyl)methylamino]-2-hydroxy-propylamino}benzamidine



;

4-isopropyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxa-diazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzene-sulfonamide gives

4-{3-[(4-isopropylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

3-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(3-trifluoromethylbenzenesulfonyl)methyl-amino]-2-hydroxypropylamino}benzamidine, acetate, FAB 431;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}phenylvinylsulfon-amide gives

4-{3-[(phenylethylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 413;

6-chloro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(6-chloro-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 447;

4-propyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-propylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

4-methoxy-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-methoxybenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 393;

2,4,6-trimethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(2,4,6-trimethylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 405;

5-{5-[(benzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives

4-{3-[(benzoylmethylamino]-2-hydroxypropylamino}-benzamidine;

5-{5-[(2-naphthylcarbonylmethylamino)methyl]-2-oxo-oxazolidin-3-yl}benzamidine gives

4-{3-[(2-naphthylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(cyclohexylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(cyclohexylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(4-biphenylylcarbonylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(4-biphenylylcarbonylmethylamino]-2-hydroxypropylamino}benzamidine;

5-{5-[(4-chlorobenzoylmethylamino)methyl]-2-oxooxazolidin-3-yl}benzamidine gives
4-{3-[(4-chlorobenzoylmethylamino]-2-hydroxypropylamino}benzamidine;

4-(1,1-dimethylpropyl)-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(4-(1,1-dimethylpropyl)benzenesulfonyl)-methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 433;

3,4-difluoro-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(3-fluoro-4-methoxybenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 411;

4-tert-butyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives
4-{3-[(4-tert-butylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 419;

4-trifluoromethyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-benzenesulfonamide gives

4-{3-[(4-trifluoromethylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 431;

4-pentyl-N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}benzenesulfonamide gives

4-{3-[(4-pentylbenzenesulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 433;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-1-naphthylsulfonamide gives

4-{3-[(1-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 413;

6-chloro-N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(6-chloro-2-naphthylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine;

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-4-biphenylylsulfonamide gives

4-{3-[(4-biphenylylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine;

N-butyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-2-naphthylsulfonamide gives

4-{3-[(2-naphthylsulfonyl)butylamino]-2-hydroxypropylamino}benzamidine.

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-(7-methoxy-2-naphthyl)sulfonamide gives

4-{3-[(7-methoxy-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 443;

N-methyl-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-phenyl]-2-oxooxazolidin-5-ylmethyl}-(6-methoxy-2-naphthyl)sulfonamide gives

4-{3-[(6-methoxy-2-naphthylsulfonyl)methylamino]-2-hydroxypropylamino}benzamidine, acetate, FAB 443.

Example 11

A solution of 10.9 g of 3-(4-cyanophenyl)-5-hydroxymethyloxazolidin-2-one ("F"), 5.9 g of 3-cyanophenol, 26.2 g of triphenylphosphine and 13.1 g of diethyl azodicarboxylate in 250 ml of THF is stirred under an atmosphere of protective gas for 4 hours. Customary work-up gives 3-(4-cyanophenyl)-5-[(3-cyanophenoxy)-methyl]oxazolidin-2-one.

A solution of 8.5 g of the dicyano compound, 5.5 g of hydroxylammonium chloride and 11.2 g of sodium carbonate in 130 ml of DMF is stirred at 60°C for 3 hours. Customary work-up gives 3-(4-N-hydroxyamidino-phenyl)-5-[(3-N-hydroxyamidinophenoxy)methyl]-oxazolidin-2-one.

Similarly to Example 2, by hydrogenation, this gives the compound 3-(4-amidinophenyl)-5-[(3-amidinophenoxy)methyl]oxazolidin-2-one, diacetate, m.p. 159-160°C, FAB 354.

Similarly, reaction of "F"

with 4'-hydroxybiphenyl-4-carbonitrile, reaction with hydroxylammonium chloride and reduction gives the compound

3-(4-amidinophenyl)-5-[(4'-amidino-4-biphenylyl-oxy)methyl]oxazolidin-2-one, diacetate, m.p. 214-224°C;

with 4-cyanophenol, reaction with hydroxylammonium chloride and reduction gives the compound

3-(4-amidinophenyl)-5-[(4-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 164°C (decomposition);

with 4-cyano-N-(ethoxycarbonyl)benzenesulfonamide gives the compound

N-[3-(4-cyanophenyl)-2-oxooxazolidin-5-ylmethyl]-N-ethoxycarbonyl-4-cyanobenzenesulfonamide, diacetate, FAB 489.

Example 12

A solution of 400 mg of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate, 240 mg of phenylpiperazine and 120 mg of sodium bicarbonate in 10 ml of acetonitrile is heated at 80°C for 18 hours. Customary work-up gives 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-phenylpiperazin-1-ylmethyl)oxazolidin-2-one.

By hydrogenation similarly to Example 2, this gives

4-[2-oxo-5-(4-phenylpiperazin-1-ylmethyl)oxazolidin-3-yl]benzamidine, acetate, FAB 380.

Similarly, the reaction of "A" with 5-bromomethylbenzo-[2,1,3]-thiadiazole gives the compound

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-ylmethyl)piperazin-1-ylmethyl]oxazolidin-2-one.

By hydrogenation similarly to Example 2, this gives

4-{2-oxo-5-[4-(benzo-[2,1,3]-thiadiazol-5-ylmethyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 512.

Similarly, reaction of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate

with 2-piperazin-1-ylpyrimidine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyrimidin-2-yl)piperazin-1-ylmethyl]oxazolidin-2-one,

with benzylpiperazine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-benzylpiperazin-1-ylmethyl]oxazolidin-2-one,

with (benzo-[2,1,3]-thiadiazol-5-yl)piperazine gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-yl)piperazin-1-ylmethyl]oxazolidin-2-one.

Similarly to Examples 3 and 4, the cleavage of the oxazolidinone ring and the oxadiazole ring

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyrimidin-2-yl)piperazin-1-ylmethyl]oxazolidin-2-one gives
4-[2-hydroxy-3-(4-pyrimidin-2-ylpiperazin-1-yl)-propylamino]benzamidine, acetate, FAB 356;

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-benzylpiperazin-1-ylmethyl]oxazolidin-2-one gives
4-[2-hydroxy-3-(4-benzylpiperazin-1-yl)propylamino]benzamidine, acetate, FAB 368;

of 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(benzo-[2,1,3]-thiadiazol-5-yl)piperazin-1-ylmethyl]-oxazolidin-2-one gives
4-[2-hydroxy-3-(4-(benzo-[2,1,3]-thiadiazol-5-yl)-piperazin-1-yl)propylamino]benzamidine, trifluoroacetate, FAB 412.

4-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(3,5-dimethoxybenzyl)piperazin-1-ylmethyl]oxazolidin-2-one gives

4-{2-hydroxy-3-[4-(3,5-dimethoxybenzyl)piperazin-1-yl]propylamino}benzamidine, FAB 428.

Similarly, reaction of methyl {3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}methanesulfonate with 4-piperazin-1-ylpyridine gives

3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(pyridin-4-yl)piperazin-1-ylmethyl}oxazolidin-2-one which is converted by hydrogenation into

3-{2-oxo-5-[4-(pyridin-4-yl)piperazin-1-ylmethyl]-oxazolidin-3-yl}benzamidine, acetate, FAB 381, m.p. 152-165 (decomp.).

Example 13

A solution of 200 mg of "A" and 66 mg of butyl isocyanate in 10 ml of dichloromethane is stirred for 4 hours. 400 mg of aminomethylpolystyrene are added, and the mixture is stirred for a further 12 hours. The polystyrene and solvent are removed, giving, after customary work-up, 3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one.

Similarly, reaction of "A"

with cyclohexyl isocyanate gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclohexylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one;

with 4-methoxyphenyl isocyanate gives

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 4-trifluoromethylphenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-trifluoromethylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

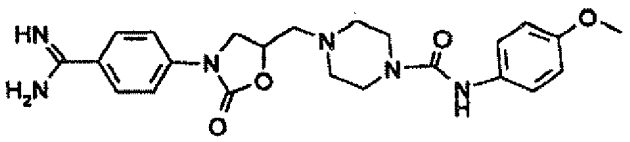
with 4-chlorophenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-chlorophenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 3-ethoxycarbonylphenyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(3-ethoxycarbonylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one;

with 1-naphthyl isocyanate gives
3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one.

By hydrogenation similarly to Example 2,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives
4-{2-oxo-5-{4-[N-(4-methoxyphenyl)aminocarbonyl]-piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 453



;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-trifluoromethylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(4-trifluoromethylphenyl)aminocarbonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 473;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(4-chlorophenyl)aminocarbonyl]piperazin-1-ylmethyl}-oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(4-chlorophenyl)aminocarbonyl]-piperazin-1-ylmethyl}oxazolidin-3-yl}benzamidine, acetate, FAB 457;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one gives

4-[2-oxo-5-(4-butylaminocarbonylpiperazin-1-yl-methyl)oxazolidin-3-yl]benzamidine, acetate, FAB 403;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-{4-[N-(3-ethoxycarbonylphenyl)aminocarbonyl]piperazin-1-yl-methyl}oxazolidin-2-one gives

4-{2-oxo-5-{4-[N-(3-ethoxycarbonylphenyl)amino-carbonyl]piperazin-1-ylmethyl}oxazolidin-3-yl}benz-amidine, acetate, FAB 495;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

4-{2-oxo-5-[4-(naphth-1-ylaminocarbonyl)piperazin-1-ylmethyl]oxazolidin-3-yl}benzamidine, acetate, FAB 403.

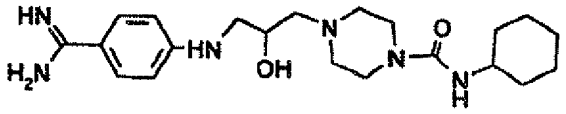
Similarly to Examples 3 and 4,

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-(4-butylaminocarbonylpiperazin-1-ylmethyl)oxazolidin-2-one gives

4-[3-(4-butylaminocarbonylpiperazin-1-yl)-2-hydroxypropylamino]benzamidine, acetate, FAB 377;

3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-5-[4-(cyclohexylaminocarbonyl)piperazin-1-ylmethyl]-oxazolidin-2-one gives

4-{3-(4-cyclohexylaminocarbonylpiperazin-1-yl)-2-hydroxypropylamino}benzamidine, acetate, FAB 403



Example 14

A solution of 1 equivalent of methyl {3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl}-methanesulfonate, 3 equivalents of glycine benzyl ester, methanesulfonate, and 3 equivalents of sodium bicarbonate in acetonitrile is heated under reflux for 18 hours. Customary work-up gives benzyl{{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}amino}acetate ("G").

Similarly to Example 1, reaction of "G" with 6-chloronaphth-2-ylsulfonyl chloride gives

benzyl {N-[6-chloronaphth-2-ylsulfonyl]-N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl}-2-oxo-oxazolidin-5-ylmethyl}amino}acetate.

By hydrogenation similarly to Example 2, this gives

{N-[6-chloronaphth-2-ylsulfonyl]-N-[3-(4-amidino-phenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 517,

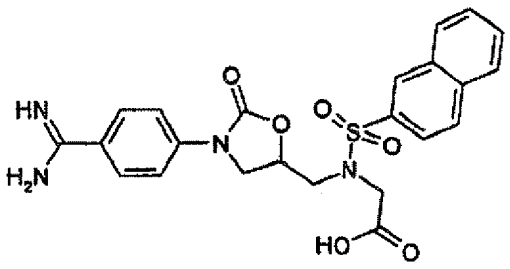
and

benzyl {N-[6-chloronaphth-2-ylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}-acetate.

Similarly, reaction of "G"

with naphth-2-ylsulfonyl chloride and subsequent hydrogenation gives

{N-[naphth-2-ylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 483



with 4-methoxybenzenesulfonyl chloride and subsequent hydrogenation gives

{N-[4-methoxybenzenesulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 453;

with phenylvinylsulfonyl chloride and subsequent hydrogenation gives

benzyl {N-[phenylvinylsulfonyl]-N-[3-(4-aminophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetate, acetate, FAB 549;

with 4-biphenylylsulfonyl chloride and subsequent hydrogenation gives

{N-[4-biphenylylsulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetic acid, acetate, FAB 509;

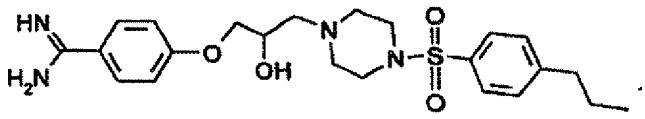
with 4-propylbenzenesulfonyl chloride and subsequent hydrogenation gives

benzyl {N-[4-propylbenzenesulfonyl]-N-[3-(4-amidinophenyl)-2-oxooxazolidin-5-ylmethyl]amino}acetate, acetate, FAB 565.

Example 15

A solution of 4-oxiranylmethoxybenzonitrile and BOC-piperazine in methanol is stirred under reflux for 4 hours. Customary work-up gives 4-[2-hydroxy-3-(4-BOC-piperazin-1-yl)propoxy]benzonitrile. The subsequent reaction with hydroxylamine hydrochloride affords N-hydroxy-4-[2-hydroxy-3-(4-BOC-piperazin-1-yl)propoxy]-benzamidine. Subsequent acylation with acetic anhydride gives 2-acetoxy-1-(4-BOC-piperazin-1-yl)-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propane. After removal of the BOC group with HCl in dioxane, reaction with 4-propylphenylsulfonyl chloride gives the compound 2-acetoxy-1-[4-(4-propylphenylsulfonyl)piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propane. Reaction similarly to Examples 3 and 4 gives the compound

4-{2-hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine



The compounds below are obtained similarly

3-{2-hydroxy-3-[4-(4-biphenylylcarbonyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 459;

3-{2-hydroxy-3-[4-(6-chloro-2-naphthylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 503;

3-{2-hydroxy-3-[4-(2-naphthylsulfonyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 469;

3-{2-hydroxy-3-[4-(4-propylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 461;

3-{2-hydroxy-3-[4-(4-isopropylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 461;

3-{2-hydroxy-3-[4-(4-methoxyphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 449;

3-{2-hydroxy-3-[4-(4-butylphenylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 399;

3-{2-hydroxy-3-[4-benzoylpiperazin-1-yl]propoxy}-benzamidine, acetate, FAB 383;

3-{2-hydroxy-3-[4-(7-methoxy-2-naphthylsulfonyl)-piperazin-1-yl]propoxy}benzamidine, acetate, FAB 499;

3-{2-hydroxy-3-[4-(3,5-dimethoxybenzyl)piperazin-1-yl]propoxy}benzamidine, acetate, FAB 429;

3-{2-hydroxy-3-[4-(4-biphenylylsulfonyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 495;

3-{2-hydroxy-3-[4-(naphth-2-ylmethyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 419;

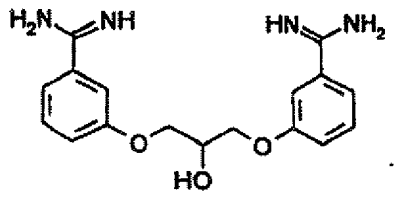
3-{2-hydroxy-3-[4-(2-naphthylcarbonyl)piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 433;

3-{2-hydroxy-3-[4-(4-biphenyl-4-ylmethyl)-piperazin-1-yl]propoxy}benzamidine, diacetate, FAB 445.

Example 16

10.0 g of 3-oxiranylmethoxybenzonitrile ("H") and 7.1 g of 3-cyanophenol together with 173 mg of caesium fluoride are molten at 130°C. Customary work-up gives 11.8 g of 1,3-bis-(3-cyanophenoxy)-2-hydroxypropane. Subsequent reaction with hydroxylammonium chloride gives 1,3-bis-[3-(N-hydroxyamidino)phenoxy]-2-hydroxy-

propane. Hydrogenation similarly to Example 2 gives 1,3-bis-(3-amidinophenoxy)-2-hydroxypropane, diacetate, FAB 329



Similarly, the compounds

1,3-bis-(4-amidinophenoxy)-2-hydroxypropane, diacetate, FAB 329

and

1-(3-amidinophenoxy)-3-(4-amidinophenoxy)-2-hydroxypropane, are obtained.

Similarly, reaction of "H" with the phenols below

4-chlorophenol,
4-methylphenol,
phenol,
4-methoxyphenol,
4-cyclohexylphenol

and subsequent reaction with hydroxylammonium chloride and hydrogenation

gives the compounds below

1-(3-amidinophenoxy)-2-hydroxy-3-(4-chlorophenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-(4-methylphenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-phenoxypropane,

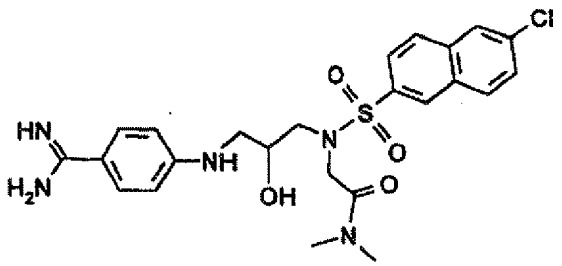
1-(3-amidinophenoxy)-2-hydroxy-3-(4-methoxyphenoxy)propane,

1-(3-amidinophenoxy)-2-hydroxy-3-(4-cyclohexyl-phenoxy)propane.

Example 17

A solution of 1 equivalent of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-yl-methyl}-(6-chloro-2-naphthyl)sulfonamide ("I") [obtainable by reaction of 5-aminomethyl-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl[oxazolidin-2-one with 6-chloro-2-naphthylsulfonyl chloride], 1.1 equivalents each of N,N'-dimethylchloroacetamide and caesium carbonate in DMF is stirred at room temperature for 12 hours. Customary work-up gives 2-((6-chloro-2-naphthylsulfonyl)-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl}phenyl]-2-oxooxazolidine-5-ylmethyl}amino)-N,N'-dimethylacetamide.

Similarly to Examples 3 and 4, this gives the compound 2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dimethylacetamide



Similarly, reaction of "I" with

N,N'-diethylchloroacetamide,
N,N'-dipropylchloroacetamide,
N-phenylchloroacetamide,
N,N'-diphenylchloroacetamide and
ethyl chloroacetate

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-diethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dipropylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N-phenylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]-N,N'-dipenylacetamide and

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(6-chloro-2-naphthylsulfonyl)amino]acetic acid, acetate FAB 491.

Similarly, by reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl}-(4-isopropylphenyl)sulfonamide with

N,N'-dimethylchloroacetamide,
N,N'-diethylchloroacetamide,
N,N'-dipropylchloroacetamide,
N-phenylchloroacetamide,
N,N'-diphenylchloroacetamide,
benzyl bromide,
iodobutane,
4-chloromethyl-2-methylthiazole,
4-methoxybenzyl bromide,
ethyl chloroacetate,
ethyl 4-chlorobutyrate,
ethyl 3-chloromethylbenzoate,

ethyl 4-chloromethylbenzoate,
3,5-dimethoxybenzyl bromide,
4-(5-methyl-[1,2,4]-oxadiazol-3-yl)benzyl bromide,
3-(5-methyl-[1,2,4]-oxadiazol-3-yl)benzyl bromide and
2-fluorobenzyl bromide

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'[-dimethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-diethylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-dipropylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N-phenylacetamide,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylsulfonyl)amino]-N,N'-diphenylacetamide,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-benzylamino]propylamino}benzamidine, acetate, FAB 481,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-butylamino]propylamino}benzamidine, acetate, FAB 447,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(2-methylthiazol-4-ylmethyl)amino]propylamino}-benzamidine, acetate, FAB 502,

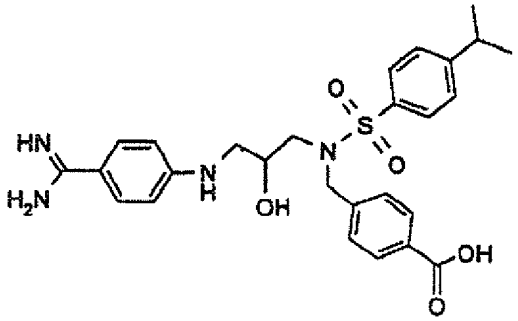
4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(4-methoxybenzyl)amino]propylamino}benzamidine, acetate, FAB 511,

2-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]acetic acid, acetate, FAB 449,

4-[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]butyric acid, diacetate, FAB 477,

3-{[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]methyl}benzoic acid, diacetate, FAB 525,

4-{[[3-(4-amidinophenylamino)-2-hydroxypropyl]-(4-isopropylbenzenesulfonyl)amino]methyl}benzoic acid, diacetate, FAB 525



4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(3,5-dimethoxybenzyl)amino]propylamino}benzamidine, diacetate, FAB 541,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(4-amidinobenzyl)amino]propylamino}benzamidine, triacetate, FAB 523,

4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(3-amidinobenzyl)amino]propylamino}benzamidine, triacetate, FAB 523 and

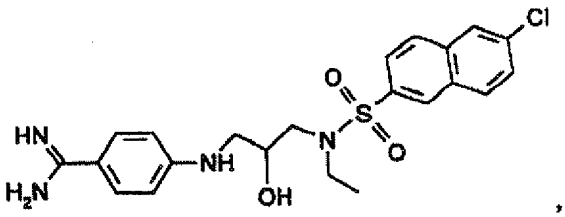
4-{(2-hydroxy)-3-[(4-isopropylbenzenesulfonyl)-(2-fluorobenzyl)amino]propylamino}benzamidine, diacetate, FAB 499.

Similarly, reaction of "I" with

iodoethane,
benzyl bromide,
4-methoxybenzyl bromide,
2-bromomethylnaphthalene,
4-chloromethyl-2-methylthiazole and
4-methoxybenzyl chloride

and subsequent cleavage of the oxazolidinone ring and the oxadiazole ring similarly to Examples 3 and 4 gives the compounds

4-{3-[(6-chloro-2-naphthylsulfonyl)ethylamino]-2-hydroxypropylamino}benzamidine



,

4-{3-[(6-chloro-2-naphthylsulfonyl)benzylamino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(4-methoxybenzyl)amino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(naphth-2-ylmethyl)amino]-2-hydroxypropylamino}benzamidine,

4-{3-[(6-chloro-2-naphthylsulfonyl)-(2-methylthiazol-4-ylmethyl)amino]-2-hydroxypropylamino}-benzamidine, diacetate, FAB 544 and

4-{3-[(6-chloro-2-naphthylsulfonyl)-(4-methoxybenzyl)amino]-2-hydroxypropylamino}benzamidine, diacetate, FAB 553.

Similarly, reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl)-(4-methoxyphenyl)sulfonamide with iodobutane and subsequent cleavage of the oxazolidinone and the oxadiazole ring similar to Example 3 and 4 gives the compound

4-{3-[(4-methoxyphenylsulfonyl)butylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 435.

Similarly, reaction of N-{3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-2-oxooxazolidin-5-ylmethyl)-(2-naphthyl)sulfonamide with

iodobutane and
iodoethane

and subsequent cleavage of the oxazolidinone and the oxadiazole ring similar to Example 3 and 4 gives the compounds

4-{3-[(2-naphthylsulfonyl)butylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 455 and

4-{3-[(2-naphthylsulfonyl)ethylamino]-2-hydroxy-propylamino}benzamidine, acetate, FAB 427.

Example 18

Similarly to Example 11, the appropriate cyano derivatives give, by reaction with hydroxylammonium chloride, the compounds below

3-(3-N-hydroxyamidinophenyl)-5-[(4-N-hydroxy-amidinophenoxy)methyl]oxazolidin-2-one, m.p. 201-205°,

3-(3-N-hydroxyamidinophenyl)-5-[(3-N-hydroxy-amidinophenoxy)methyl]oxazolidin-2-one,

3-(4-N-hydroxyamidinophenyl)-5-[(3-N-hydroxyamidinobenzyloxy)methyl]oxazolidin-2-one,

3-(3-N-hydroxyamidinophenyl)-5-[(3-N-hydroxyamidinobenzyloxy)methyl]oxazolidin-2-one.

Similarly to Example 2, these give, by hydrogenation, the compounds

3-(3-amidinophenyl)-5-[(4-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 150-166° (decomposition), FAB 354;

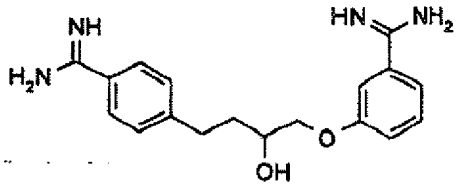
3-(3-amidinophenyl)-5-[(3-amidinophenoxy)methyl]-oxazolidin-2-one, diacetate, m.p. 312-318°;

3-(4-amidinophenyl)-5-[(3-amidinobenzyloxy)-methyl]oxazolidin-2-one, triacetate, m.p. 189-205° (decomp.), FAB 368;

3-(3-amidinophenyl)-5-[(3-amidinobenzyloxy)-methyl]oxazolidin-2-one, triacetate, m.p. 204-222° (decomp.), FAB 368.

Example 19

Similarly to Example 16, reaction of 4-oxiranylethylbenzonitrile and 3-cyanophenol, subsequent reaction with hydroxylammonium chloride and hydrogenation gives the compound 4-[3-hydroxy-4-(3-amidinophenoxy)butyl]benzamidine, diacetate, FAB 327



Example 20

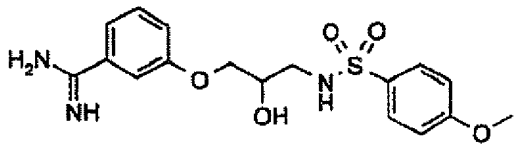
Under nitrogen, 10.0 g of 3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenol is added to 50 ml of DMF and 2.6 g of sodium hydride are subsequently added at 0°. 5.1 ml of epibromohydrin are added, and the mixture is stirred at room temperature for 24 hours. Customary work-up gives 5-methyl-3-(3-oxiranylmethoxyphenyl)-[1,2,4]-oxadiazol.

8.0 g of the oxiranyl compound are dissolved in 400 ml of methanol and NH_3 gas is introduced for 6 hours. The mixture is stirred for another 16 hours, yielding, after removal of the solvent, 1-amino-3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propan-2-ole ("AB").

500 mg of "AB" and 434 mg of 4-methoxyphenylsulfonyl chloride together with 2.0 g of polymeric DMAP (1.6 mmol of dimethylaminopyridine/g of resin) in 5 ml of pyridine are stirred at room temperature for 24 hours. The resin is filtered off and the filtrate is worked up as usual, giving N-{2-hydroxy-3-[3-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propyl}-4-methoxy-benzenesulfonamide.

This gives, by hydrogenation similarly to Example 2, the compound

3-[2-hydroxy-3-(4-methoxybenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 380



Similarly, reaction of "AB" with

4-isopropylphenylsulfonyl chloride,
2-naphthylsulfonyl chloride,
6-chloro-2-naphthylsulfonyl chloride,
7-methoxy-2-naphthylsulfonyl chloride

and subsequent hydrogenation

gives the compounds below

3-[2-hydroxy-3-(4-isopropylbenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 392;
3-[2-hydroxy-3-(2-naphthylsulfonylamino)propoxy]-benzamidine, acetate, FAB 400;
3-[2-hydroxy-3-(6-chloro-2-naphthylsulfonylamino)-propoxy]benzamidine, acetate, FAB 434;
3-[2-hydroxy-3-(7-methoxy-2-naphthylsulfonyl-amino)propoxy]benzamidine, acetate, FAB 430;

Similarly, reaction of 1-amino-3-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenoxy]propan-2-ole

with 4-methoxyphenylsulfonyl chloride,
4-isopropylphenylsulfonyl chloride,
2-naphthylsulfonyl chloride,
6-chloro-2-naphthylsulfonyl chloride,
7-methoxy-2-naphthylsulfonyl chloride

and subsequent hydrogenation

gives the following compounds

4-[2-hydroxy-3-(4-methoxybenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 380;
4-[2-hydroxy-3-(4-isopropylbenzenesulfonylamino)-propoxy]benzamidine, acetate, FAB 392;
4-[2-hydroxy-3-(2-naphthylsulfonylamino)propoxy]-benzamidine, acetate, FAB 400;
4-[2-hydroxy-3-(6-chloro-2-naphthylsulfonylamino)-propoxy]benzamidine, acetate, FAB 434;
4-[2-hydroxy-3-(7-methoxy-2-naphthylsulfonyl-amino)propoxy]benzamidine, acetate, FAB 430.

Example 21

10.7 ml of sodium methoxide (30% strength in methanol) are added to 30 ml of methanol, 4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline is added under nitrogen and the mixture is stirred at 45° for 10 minutes. The mixture is subsequently added to a suspension of 480 mg of paraformaldehyde and 20 ml of methanol, and the mixture is stirred at 60°C for 2 hours. The mixture is then admixed with 440 mg of sodium borohydride and stirred at 60° for 1 hour. The mixture is subsequently admixed two more times with 1.44 g of paraformaldehyde, 3.1 g of sodium methoxide and 220 mg of sodium borohydride each time.

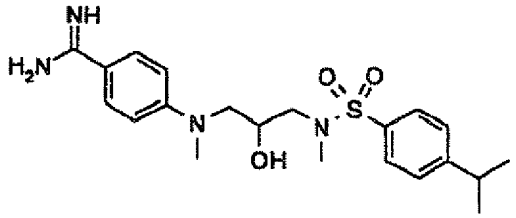
After [lacuna] hours, the mixture is hydrolyzed using 1N NaOH and worked up as usual. This gives, as a crude product, 1.93 g of N-methyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline.

A solution of 1.35 g of 4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-N-methylaniline and 1.0 ml of epichlorohydrin in 5 ml of ethanol and 3.5 ml of water is boiled under reflux for 12 hours. Customary work-up gives 0.4 g of N-methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)aniline. A solution of 0.39 g of N-methyl-N-oxiranylmethyl-4-(5-methyl-[1,2,4]-oxadiazol-3-yl)-aniline and 30 ml of methylamine (33% strength in ethanol) in 10 ml of ethanol is stirred at 65° for 15 hours. Customary work-up gives 0.44 g of 1-methylamino-3-{methyl-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]amino}propan-2-ole ("BC").

100 mg of "BC" and 87 mg of 4-isopropylphenylsulfonyl chloride together with 300 mg of polymeric DMAP (1.6 mmol of dimethylaminopyridine/g of resin) in 5 ml of dichloromethane are stirred at room temperature for 16 hours. The resin is filtered off and the filtrate is worked up as usual. This gives 109 mg of N-(2-hydroxy-3-{methyl-[4-(5-methyl-[1,2,4]-oxadiazol-3-yl)phenyl]-amino}propyl)-4-isopropyl-N-methylbenzenesulfonamide.

By hydrogenation similarly to Example 2, this gives the compound

4-({2-hydroxy-3-[(4-isopropylbenzenesulfonyl)-N-methylamino]propyl}-N-methylamino)benzamidine, acetate, FAB 419



Similarly, reaction of "BC" with 2-naphthylsulfonyl chloride and subsequent hydrogenation gives the compound

4-({2-hydroxy-3-[(naphth-2-ylsulfonyl)-N-methyl-amino]propyl}-N-methylamino)benzamidine, diacetate, FAB 427.

The following examples relate to pharmaceutical formulations:

Example A: injection vials

A solution of 100 g of an active compound of the formula I and 5 g of disodium hydrogen phosphate in 3 l of doubly distilled water is brought to pH 6.5 with 2 N hydrochloric acid and subjected to sterile filtration, and injection vials are filled with the solution, lyophilized under sterile conditions and closed under sterile conditions. Each injection vial contains 5 mg of active compound.

Example B: suppositories

A mixture of 20 g of an active compound of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and allowed

to cool. Each suppository contains 20 mg of active compound.

Example C: solution

A solution is prepared from 1 g of an active compound of the formula I, 9.38 g of $NaH_2PO_4 \cdot 2H_2O$, 28.48 g of $Na_2HPO_4 \cdot 12H_2O$ and 0.1 g of benzalkonium chloride in 940 ml of doubly distilled water. It is brought to pH 6.8, topped up to 1 l and sterilized by irradiation. This solution can be used in the form of eyedrops.

Example D: ointment

500 g of an active compound of the formula I are mixed with 99.5 g of vaseline under aseptic conditions.

Example E: tablets

A mixture of 1 kg of active compound of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is pressed into tablets in the customary manner such that each tablet contains 10 mg of active compound.

Example F: coated tablets

Tablets are pressed analogously to Example E and are then coated in the customary manner with a coating of sucrose, potato starch, talc, tragacanth gum and dyestuff.

Example G: capsules

Hard gelatin capsules are filled with 2 kg of active compound of the formula I in the customary manner such that each capsule contains 20 mg of the active compound.

Example H: ampoules

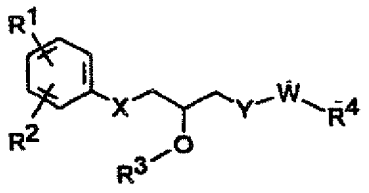
A solution of 1 kg of active compound of the formula I in 60 l of doubly distilled water is subjected to sterile filtration, and ampoules are filled with the solution, lyophilized under sterile conditions and

closed under sterile conditions. Each ampoule contains 10 mg of active compound.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgement or any form of suggestion that the prior art forms part of the common general knowledge in Australia.

The claims defining the invention are as follows:

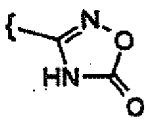
1. Compounds of the formula I



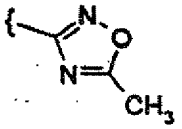
I

in which

R^1 is $-C(=NH)-NH_2$ which can also be mono-substituted by -COA, $-CO-[C(R^5)_2]_n-Ar$, -COOA, -OH or by a conventional amino-protective group,



or



R^2 is H, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NR^5COA, NHCOAr, $NHSO_2A$, $NHSO_2Ar$, $COOR^5$, $CON(R^5)_2$, CONHAr, COR^5, COAr, $S(O)_nA$ or $S(O)_nAr$,

R^3 is R^5 or $-[C(R^5)_2]_m-COOR^5$,

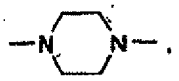
R^3 and X together are also -CO-N-, thus forming a 5-membered ring, where R^3 is -C=O and X is N

R^4 is A, cycloalkyl, $-[C(R^5)_2]_nAr$, $-[C(R^5)_2]_nHet$ or $-CR^5=CR^5-Ar$,

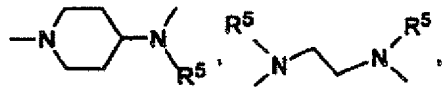
R^5 is H, A or benzyl,

X is O, NR^5 or CH_2,

Y is O, NR^5, $N[C(R^5)_2]_n$-Ar, $N[C(R^5)_2]_n$-Het,



$N[C(R^5)_2]_n$-$COOR^5$,



$N[C(R^5)_2]_n$-$CON(R^5)_2$, $N[C(R^5)_2]_n$-$CONR^5Ar$ or $N[C(R^5)_2]_n$-$CONAr_2$,

W is a bond, $-SO_2-$, -CO-, or $-CONR^5-$,

A is alkyl having 1-20 C atoms in which one or two CH_2 groups can be replaced by O or S atoms or by $-CR^5=CR^5-$ groups and/or 1-7 H atoms can be replaced by F,

Ar is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, Ar', OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, NHCOAr', $NHSO_2A$, $NHSO_2Ar'$, $COOR^5$, $CON(R^5)_2$, CONHAr', COR^5, COAr', $S(O)_nA$ or $S(O)_nAr$,

Ar' is naphthyl or phenyl which is unsubstituted or mono-, di- or trisubstituted by R^1, A, OR^5, $N(R^5)_2$, NO_2, CN, Hal, NHCOA, $COOR^5$, $CON(R^5)_2$, COR^5 or $S(O)_nA$,

Het is a mono- or bicyclic saturated or unsaturated heterocyclic ring system which contains one, two, three or four identical or different hetero atoms such as nitrogen, oxygen and sulfur and which is unsubstituted or mono- or polysubstituted by Hal, A, Ar', OR^5, $COOR^5$, CN, $N(R^5)_2$, NO_2, NHCOA, NHCOAr' and/or carbonyl oxygen,

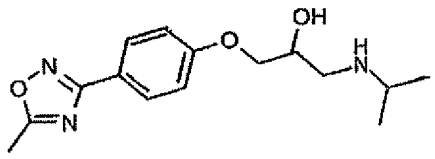
Hal is F, Cl, Br or I,

m is 0, 1, 2, 3 or 4,

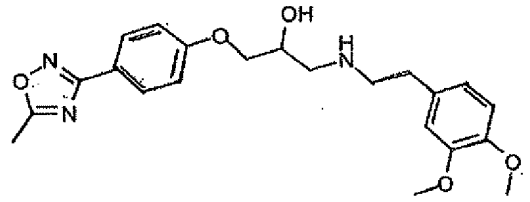
n is 0, 1 or 2,

and salts thereof,

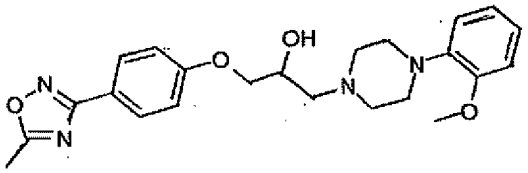
with the proviso that the following compounds are excluded:



1-isopropylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol;



1-[2-(3,4-dimethoxy-phenyl)-ethylamino-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol; and



1-[4-(2-methoxy-phenyl)-piperazin-1-yl]-3-[4-(5-methyl-[1,2,4]oxadiazol-3-yl)-phenoxy]-propan-2-ol.

2. Compounds according to Claim 1,

a) 4-{3-[4-(2,6-dichloro-4-methoxybenzene-sulfonyl)piperazin-1-yl]-2-hydroxypropyl-amino}benzamidine;

b) 4-{3-[(4-isopropylbenzenesulfonyl)methyl-amino]-2-hydroxypropylamino}benzamidine;

c) 4-{3-[4-(1-naphthylbenzenesulfonyl)piperazin-1-yl]-2-hydroxypropylamino}benzamidine;

d) 3-(4-amidinophenyl)-5-[(3-amidinophenoxy)-methyl]oxazolidin-2-one

and salts thereof.

3. Process for preparing compounds of the formula I according to Claim 1 and salts thereof, characterized in that

a) they are liberated from one of their functional derivatives by treatment with a solvolysing or hydrogenolysing agent, by

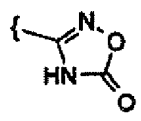
i) liberating an amidino group from its oxadiazole derivative by hydrogenolysis,

ii) replacing a conventional amino-protective group by treatment with a solvolysing or hydrogenolysing agent with hydrogen or liberating an amino group which is protected by a conventional protective group,

or

b) that for preparing compounds of the formula I

in which R^1 is



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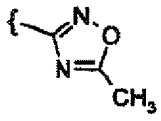
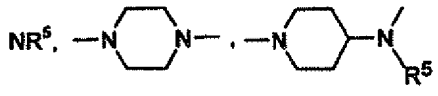


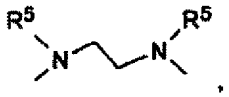
,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is



or

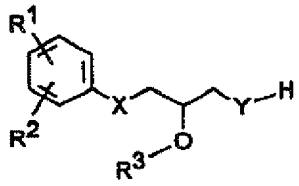


,

W is $-SO_2-$ or -CO-,

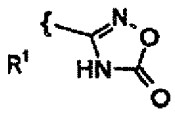
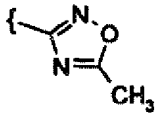
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II

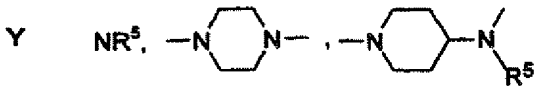


II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is 

or

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula III

$$R^4\text{-}W\text{-}L \qquad III$$

in which

W is $-SO_2-$ or -CO-,

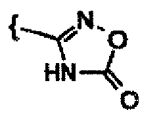
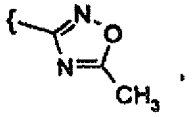
R^4 is as defined in Claim 1,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

or

c) that for preparing compounds of the formula I

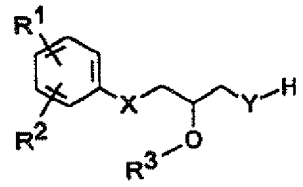
in which R^1 is


or

,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
W is a bond,

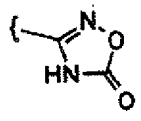
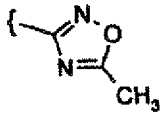
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II


II

in which

R^1 is

R^1 
or

.

R^3 and X together are -CO-N-, thus forming a 5-membered ring,
Y is O,
and R^2 is as defined in Claim 1,

is reacted with a compound of the formula IV

R^4-W-OH IV

in which

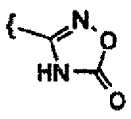
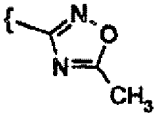
W is a bond,

and R^4 is as defined in Claim 1,

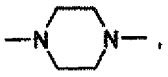
or

d) that for preparing compounds of the formula I

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is  ,

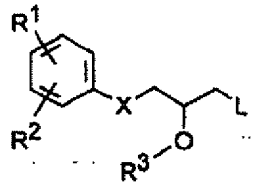
W is a bond,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$,

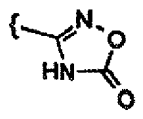
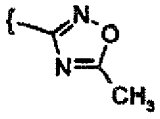
m is 0,

and R^2 is as defined in Claim 1,

a compound of the formula V

 V

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

and L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^2 is as defined in Claim 1,

is reacted with a compound of the formula VI

$$R^4\text{-}W\text{-}Y\text{-}H \qquad VI$$

in which

W is a bond,

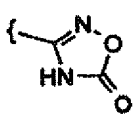
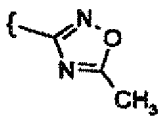
Y is  ,

R^4 is $-[C(R^5)_2]_mAr$ or $-[C(R^5)_2]_mHet$ and

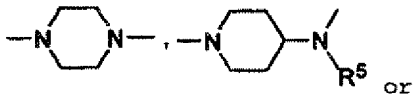
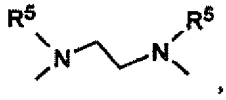
m is 0,

or

e) that for preparing compounds of the formula I in which

R^1 is  or  ,

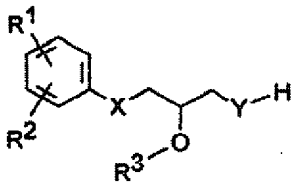
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is NR^5,  or  ,

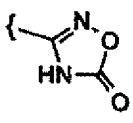
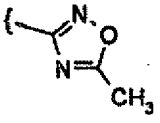
W is -CONH-,

and R^2 and R^4 are as defined in Claim 1,

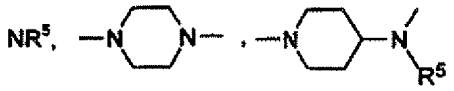
a compound of the formula II

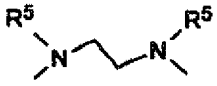
 II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is 

or 

and R^2 and R^5 are as as defined in Claim 1,

is reacted with a compound of the formula VII

$$R^4\text{-}N{=}C{=}O \qquad \text{VII}$$

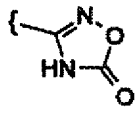
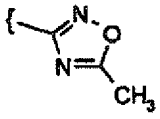
in which

R^4 is as defined in Claim 1,

or

f) that for preparing compounds of the formula I

in which

R^1 is  or  ,

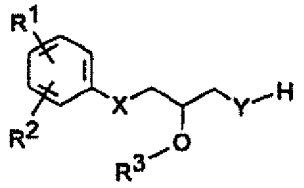
R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m\text{-}COOR^5$,

W is SO_2,

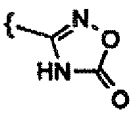
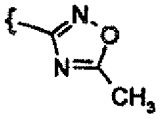
and R^2 and R^4 are as defined in Claim 1,

a compound of the formula II



II

in which

R^1 is  or  ,

R^3 and X together are -CO-N-, thus forming a 5-membered ring,

Y is $N[C(R^5)_2]_m$-$COOR^5$,

and R^2 and R^5 are as defined in Claim 1,

is reacted with a compound of the formula VIII

$$R^4\text{-}SO_2\text{-}L \qquad \text{VIII}$$

in which

L is Cl, Br, I or a free or a reactive functionally derivatized OH group,

and R^4 is as defined in Claim 1,

or

g) that for preparing compounds of the formula I

in which

X is NH and

R^3 is H

and R^1, R^2, R^4, Y and W are as defined in Claim 1,

these compounds are liberated from their oxazolidinone derivatives by treatment with a solvolysing or hydrogenolyzing agent,

or

h) that for preparing compounds of the formula I

in which R^1 is $-C(=NH)-NH_2$,

a cyano group is converted into an amidino group,

or

I) in a compound of the formula I, one or more radicals Y, R^1, R^2, R^3 and/or R^4 are converted into one or more radicals R^1, R^2, R^3 and/or R^4,

by, for example,

i) hydrolysing an ester group to give a carboxyl group,

ii) reducing a nitro group,

iii) acylating an amino group,

and/or

k) converting a base or acid of the formula I into one of its salts.

4. Process for preparing pharmaceutical formulations, characterized in that a compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts is brought into a suitable dosage form together with at least one solid, liquid or semi-liquid carrier or auxiliary.

5. Pharmaceutical formulation, characterized by a content of at least one compound of the formula I according to Claim 1 and/or one of its physiologically acceptable salts together with at least one solid, liquid or semi-liquid carrier or auxiliary.

6. Use of compounds of the formula I according to Claim 1 and their physiologically acceptable salts for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

7. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the preparation of a medicament.

8. Use of compounds of the formula I according to Claim 1 and/or their physiologically acceptable salts for the preparation of a medicament for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens.

9. Method for combating thromboses, myocardial infarction, arteriosclerosis, inflammations, apoplexy, angina pectoris, restenosis after angioplasty and claudicatio intermittens which comprises administering to a subject in need of such treatment at least one compound of the formula I according to claim 1 and/or one of its physiologically acceptable salts together with at least one solid, liquid or semi-liquid carrier or auxiliary.

10. Compounds of the formula I, processes for their preparation or pharmaceutical compositions or methods of treatment involving/containing them, substantially as hereinbefore described with reference to the Examples.

DATED this 30th day of April, 2001

MERCK PATENT GMBH

By its Patent Attorneys

DAVIES COLLISON CAVE